COMPUTER-BASED MODEL FOR IDENTIFICATION AND CHARACTERIZATION OF NON-COMPETITIVE INHIBITORS OF NICOTINIC ACETYLCHOLINE RECEPTORS AND RELATED LIGAND-GATED ION CHANNEL RECEPTORS

The present application is a Continuation-In-Part of U.S. Application No. 10/411,206, filed April 11, 2003, the entire contents of which are hereby incorporated by reference and for which priority is claimed under 35 U.S.C. § 120.

The present application includes an appended Sequence Listing of 15 amino acid sequences and Appendices 1 to 5 providing computer programming scripts, parameter files and atomic coordinates of computer models of the luminal channel portion of the ligand-gated ion channel subtypes.

FIELD OF THE INVENTION

The present invention relates to a computer system for generating molecular models of ligand-gated ion channels and in particular, molecular models of the inner lumen of a ligand-gated ion channel and associated binding pockets. The present invention further relates to a computer system simulating interaction of the computer-based model of the ligand-gated channel and non-competitive inhibitor compounds for identification and characterization of non-competitive inhibitors and to inhibitor compounds so discovered. The present invention also relates to methods for treating various disorders related to ligand-gated ion channel receptor function. The invention also provides a way to examine compounds for "off-target" activity that may cause undesirable side effects to a desired target activity or that may represent a new therapeutic activity for a known compound.

BACKGROUND OF THE INVENTION

Ligand gated ion channels (LGICs) are currently very important targets for drug discovery in the pharmaceutical industry. The superfamily is separated into the nicotinic receptor superfamily (muscular and neuronal nicotinic, GABA-A and-C, glycine and 5-HT3 receptors), the excitatory amino acid superfamily (glutamate, aspartate and kainate receptors) and the ATP purinergic ligand gated ion channels. These families only differ in the number of transmembrane domains found in each subunit (nicotinic – 4 transmembrane domains, excitatory amino acid receptors – 3 transmembrane domains, ATP purinergic LGICs – 2 transmembrane domains).

Nicotinic acetylcholine receptors (nAChRs) are a family of ligand gated ion channels that control the fast permeation of cations through the postsynaptic cell membrane when stimulated by acetylcholine. Physiologically, nAChRs are key targets in drug discovery for a number of diseases, including Alzheimer's and Parkinson's disease, and have been widely discussed and investigated.

Structural and functional studies of nAChRs have led to the elucidation of three physiological states of the receptor: 1) resting (channel closed); 2) acetylcholine stimulated (channel open); and 3) a desensitized state where the ion flux is inhibited even in the presence of neurotransmitter. The overall structure of nicotinic acetylcholine receptor of *Torpedo marmorata* has been examined by Unwin and coworkers using cryo-electron microscopy and revealed the conical shape of the channel portion of the receptor and the relationship of the membrane-spanning helices to each other (see Figure 1). In spite of these unprecedented advances in resolving the structures of transmembrane proteins, the detailed, atomic resolution, structure of the entire nAChR family remains unresolved.

Muscular nAChRs are located at the nerve-muscle junctions and are responsible for triggering motor motion, and neuronal nAChRs, widely

distributed in the nervous system, are involved in the fast synaptic transmission of inter-neuronal communication. It is known that these receptors are structurally similar in their overall composition but differ in the exact make-up of the protein subunits forming the receptors.

The nicotinic acetylcholine receptor (nAChR) is presently the best characterized member of the ligand-gated ion channel superfamily. The nicotinic receptors are of great therapeutic importance. The subunits assemble combinatorily to form a variety of pentameric transmembrane protein subtypes.

Each receptor is formed by bringing together five separate trans-membrane proteins, each containing a large extra-cellular N-terminal domain, four membrane spanning alpha helices (M1, M2, M3, and M4) and a small C-terminal domain (see Figure 1). Two, homologous, neurotransmitter binding sites are formed by the N-terminal domains where cholinergic agonist and competitive antagonists bind, and are the usual targets for drug design. The ion channel is formed by a pentameric arrangement of the M2 helical segments contributed by the five proteins (see Figure 2). The channel specificity, characteristic of each receptor subtype, is controlled by the identity of each of the M2 helices.

Neuronal nicotinic acetylcholine receptors (nAChRs) are the class of ligand-gated ion channels of the central and peripheral nervous system that regulate synaptic activity. The basic structure of the nAChR is shown in Figures 1 and 2. Referring to Figure 1, nAChR consists of five transmembrane subunits 1, 2, 3, 4, 5 oriented around a central pore 6 permeable to cations. Cations flow through the pore is regulated by ligand binding. The subunits in nAChR are typically α subunits and β subunits.

At present, 12 different homologous subunits have been identified in neuronal nAChRs, 9 α subunits (α2-α10) and 3 β subunits (β2-β4). The major difference between α and β subunits is the presence and location of the disulfide bond formed by two adjacent cysteines in the α systems, the absence of this feature distinguishes non-α subunits. This disulfide bond

located on the extracellular domain plays an important role in neurotransmitter binding as well as the mechanism of channel opening. These subunits combine to form multiple nAChR subtypes and predominant stoichiometry is $(\alpha)_2(\beta)_3$, however pentamers containing only α subunit are also known e.g., $(\alpha 7)_5$. In case of muscular nAChR the stoichiometry is more complicated, the muscular nAChR receptor is predominantly described as $(\alpha)_2\beta\delta\gamma$.

The nAChRs are very complex systems with dozens of potential different binding domains for different classes of compounds of both endo- and exogenous origin (Arias H.R., (1997) Topology of ligand binding sites on the nicotinic acetylcholine receptor. *Brain Res. Rev.* 25: 133-91). Two primary cholinergic binding sites are located on the extracellular side 7 (refer to Figure 1, approximately 30-35 Å above the membrane) in the pocket at the interface between the α and β subunits. The nAChR contains several other classes of binding sites at which non-competitive inhibitors (NCIs) bind (Arias H.R. (1998) Binding sites for exogenous and endogenous non-competitive inhibitors of the nicotinic acetylcholine receptor. *Biochim. Biophys. Act.* 1376: 173-220). One, so-called "luminal high affinity" NCI binding domain is located on the surface of the internal lumen forming the ion channel. This site is a highly polar and negatively charged domain, which primarily plays the role as a cation selector. In general, an NCI compound does not compete with the neurotransmitter ligand of the receptor for binding to the neurotransmitter ligand binding site of the receptor located on the external surface both α subunits in a pocket approximately 30-35 Å from the transmembrane portion of the subunit (that is, above the surface membrane when the receptor is expressed on in a cell), as described by Arias [Arias, H.R. (2000) Localization of agonist and competitive antagonist binding sites on nicotinic acetylcholine receptors *Neurochem. Int* 36, 595-645].

Such drugs as mecamylamine, ketamine, bupropion or barbiturates bind in the narrowest region of the channel on the cell membrane level.

Inhibitors acting there are mainly amines. It is believed that the ligands bind into this region and sterically plug the channel, blocking the flux of ions.

"Non-luminal" sites are the population of 10-30 binding sites located mostly at the lipid-protein interface for which an allosteric mechanism of non-competitive inhibition was proposed. Agents of different origin (steroids, fatty acids, alcohols, local anesthetics etc.) can bind to those sites and modulate nAChR activity.

Other classes of ligand-gated ion channels include GABA (Johnston G. A. (2002) Medicinal chemistry and molecular pharmacology of GABA(C) receptors. *Curr Top Med Chem* 2, 903-13), 5HT3 (D.C. Reeves, S.C. Lummis, (2002) The molecular basis of the structure and function of the 5-HT3 receptor: a model ligand-gated ion channel (review). *Mol. Membr. Biol.* 19, 11-26), AMPA (T.B. Stensbol, U Madsen, P. Krogsgaard-Larsen, (2002) The AMPA receptor binding site: focus on agonists and competitive antagonists. *Curr. Pharm. Des.* 8, 857-72) and NMDA (K.A. Macritchie, A.H. Young, (2001) Emerging targets for the treatment of depressive disorder. *Expert Opin. Ther. Targets* 5, 601-612) receptors, etc. Although the molecular structure of these receptors differ significantly, it is believed that the luminal domains are homologous to the luminal domain of nAChRs. There are five (or occasionally four) transmembrane helices forming the wall of the channel with "rings" of polar amino-acids exposed on the pre-forming surface and the same non-competitive inhibition phenomenon can be observed.

In summary, the luminal high affinity NCI binding domain is located on the surface of the internal lumen forming the ion channel. Drugs of different origin bind in this region and sterically plug the channel blocking the flux of ions.

Non-competitive inhibition of the nAChR can be responsible for severe adverse drug effects. On the other hand, designing ligands that specifically interact with this site can be part of the development of new

treatments of Alzheimer's and Parkinson's diseases, for example by identifying compounds likely to exhibit side effects through non-competitive inhibition of a LGIC. Furthermore, the compounds identified as NCIs by the present method are likely to find use in treating Tourette's syndrome and cognitive disorders, schizophrenia, pain [see, Lloyd, G.K. and Williams, M. (2000) *J. Pharmacol. Exper. Ther.* 292, 461-467.], anxiety, depression, neurodegeneration and addictions caused by an overactive LGIC receptor, especially diseases in which nicotine agonist activity against a neuronal nAChR is part of the etiology (e.g. smoking addiction). The invention can also be used to evaluate cardiovascular toxicity of a compound mediated by non-competitive inhibition of a LGIC receptor, e.g. arrythmia and GI spasming or diarrheal side effects of a compound caused by inhibition of a musclar nAChR.

Classical methods of NCI identification are time consuming and not effective in rapid screening of chemical libraries of drug candidates.

Several different molecular models of the nAChR transmembrane domain have been reported (Capener CE, Kim HJ, Arinaminpathy Y, Sansom MS (2002) Ion channels: structural bioinformatics and modelling. *Hum Mol Genet* 11:2425-33). However, none of those models were used to investigate interaction with channel blockers. A computer based model for *in silico* simulations of NCI interactions with the luminal domain of LGICs is needed to better understand the phenomenon of the receptor's inhibition by NCIs.

Furthermore, in drug discovery, the potential adverse effects of drug candidates are of great importance. In-depth understanding of mechanistic interaction of luminal NCIs with different subtypes of LGICs, especially of nAChRs, is required to remove potential unwanted side effects at this site. In this respect, a rapid screening technology that would identify NCIs of LGICs, and especially of nAChRs would be greatly desired.

The functional determination and characterization of a NCI of a LGIC is very complex and time consuming. One approach is affinity chromatography based on immobilized receptor protein. This is a versatile tool for investigation of intermolecular interactions of a receptor with its ligands. The chemometric approach of affinity chromatography can be employed for determination of reliable relative affinities of ligands as well as kinetic characterization, which otherwise would be inaccessible, for a large set of compounds (Kaliszan R., Wainer I.W. (1997) Combination of Biochromatography and Chemometrics: A Potential New Research Strategy in Molecular Pharmacology and Drug Design. *In* Chromatographic Separations Based on Molecular Recognition. K. Jinno, editors Wiley-VCH).

Methods using nAChR and other receptors immobilized on a chromatographic support have been elaborated (US patents 6,387,268, 6,139,735, provisional application no. 60/337,172). It was shown that the obtained stationary phases worked as selective binding materials for competitive cholinergic ligands and can be used for high throughput screening of various competitive agonists and antagonists (R. Moaddel, I.W. Wainer, (2003) Immobilized nicotinic receptor stationary phases: going with the flow in high-throughput screening and pharmacological studies *J Pharm Biomed Anal.* 30, 1715-24). The usefulness of such columns based on immobilized nAChR for investigations and modeling of NCI affinity has also been demonstrated. Using a novel non-linear chromatography approach *off* and *on* kinetics of ligand interaction with the receptor can be determined. (K. Jozwiak, J.Haginaka et al., (2002) Displacement and nonlinear chromatographic techniques in the investigation of interaction of noncompetitive inhibitors with an immobilized $\alpha 3\beta 4$ nicotinic acetylcholine receptor liquid chromatographic stationary phase. *Anal Chem* 74: 4618-4624).

BRIEF DESCRIPTION OF THE DRAWINGS

The features of the invention may be better understood by reference to the drawings described below.

Figure 1 and Figure 2 schematically show the general structure of a neuronal nicotinic acetylcholine receptor (nAChR).

Figure 3 shows the luminal domain of α3β2 and α3β4 channels. Red – negatively charged (e.g., aspartic acid, glutamic acid), orange – polar (e.g., serine or threonine), green – hydrophobic (e.g., leucine, valine), light blue – positively charged (e.g., lysine), dark blue – aromatic (e.g., phenylalanine). Figure 3a shows a model of the α3β2 luminal domain having five helices forming the wall of the ion channel. Figure 3b shows the α3β2 luminal domain model (in ribbon and CPK rendering) in perpendicular view. Only 3 helices are shown for clarity. Figure 3c shows a model of the α3β4 luminal domain having five helices forming the wall of the ion channel. Figure 3d shows the α3β4 luminal domain model (in ribbon and CPK rendering) in perpendicular view. Again, only 3 helices are shown for clarity. The cleft formed by the substitution of phenylalanine for valine at position 15 in the helix is noted by the arrow.

Figure 4 is a schematic representation of a computer system useful in the practice of the invention.

Figure 5 is a model of luminal domain of α3β4 subtype of nAChR illustrating its electrostatic potential of the inner surface of the channel. The Figure particularly shows the electronegative potential of the cation selector region of the channel. Negative potentials are shown in red, and the positive potentials are shown in blue.

Figure 6 shows a two cluster interaction of the ligand PCP with α3β4. Generally NCIs bind into the small pocket formed on the apolar domain (Phenylalanine/Valine rings). Tested structures primarily entered a hydrophobic pocket formed between the α3 and β4 helices and subsequently interacted with protein side chains forming hydrogen bonds. Ligands most likely form two separate clusters on two symmetrical active

sites. Estimated free energies of docking are in the range of experimental IC_{50} of tested inhibitors.

Figure 7 shows example compounds tested by chromatography on an $\alpha_3\beta_4$ nAChR affinity column. Among the tested drugs are aliphatic amines like mecamylamine, amantadine, memantine and such compound like bupropion, ketamine and mk-801. Also, some examples of more complicated structures include clozapine, pcp, methadone and verapamil. Further, the structures of two enantiomers dextromethorphan and levomethorphan. Finally, there is a structure for ethidium: the only compound permanently ionized and that binds to its specific site.

Figure 8 shows the mecamylamine binding to the luminal domain of $\alpha3\beta4$.

Figure 9 shows the MK-801 binding to the luminal domain of $\alpha3\beta4$.

Figure 10 shows a correlation of log k' (chromatographic) with log $(1/k_i)$ (docking simulation).

Figure 11 shows the enantioselectivity of the dextromethorphan/levomethorphan pair determined in chromatographic experiments. Dextromethorphan had a longer retention time and the profile was more asymmetric.

Figure 12 shows an overlay of the most stable docked orientations of dextromethorphan (grey) and levomethorphan (magenta) complexes with the $\alpha3\beta4$-nAChR luminal domain (Figure 12a) and the $\alpha3\beta2$-nAChR luminal domain (Figure 12b). Only two helices (one $\alpha3$ and one β) are presented for clarity. The serine residues (position 8, and also in position 12 in Figure 12a) are rendered as CPK models and colored in orange. The cleft formed by the valine to phenylalanine substitution in the $\beta4$ subtype helix is indicated by the arrow in Figure 12a and its absence is similarly indicated in Figure 12b.

Figure 13 illustrates cluster analysis according to the present invention. Three clusters were identified among tested NCIs. Cluster 1 – red, cluster, 2 – magenta, cluster 3 – green.

Figure 14 shows the synthetic scheme for novel compound DM-01; i - 1-chloroethyl chloroformate; ii – methanol; iii – 1-chloroacetone.

Figure 15 shows the NCI activity in the Rb^+ efflux assay of compound DM-01.

DETAILED DESCRIPTION OF THE INVENTION

The present invention results from understanding of the interactions between a particular subtype of the neuronal nAChRs and molecules that inhibit the flow of ions through the cell membrane. A first step in this understanding is to characterize the composition of the membrane-spanning M2 helices. So far, twelve distinct M2 helices (known as subunits of the channel), nine labeled alpha (α2-α10) and three labeled beta (β2-β4), have been shown to form channels of a wide variety of both homomeric and heteromeric subtypes of neuronal nAChRs. The most common subunit stoichiometry has been determined to be $(\alpha X)_2(\beta Y)_3$, (X = 2-4; Y = 2-4), respectively for heteromeric subtypes and $(\alpha Z)_5$, (Z = 7-10) for the homomeric subtypes. However, other, more complex, combinations have also been reported. These various subtypes have been found in different locations of the central and peripheral nervous system and can be assigned to different functions. For instance: the α4β2 and α4β4 subtypes appear to play a role in cognition, neurodegeneration, pain, anxiety and depression; the α3β2 subtype in dopamine release and Parkinson's disease; the α7 in GABA release; the α9 in auditory function and development; and the α3β4 in norepinephrine release, cardiovascular and gastrointestinal action. In addition, NCIs of ligand-gated ion channels are expected to have therapeutic benefit in treatment of cognitive dysfunction/attentional disorders such as ADHD, neurodegenerative diseases such as Alzheimer's disease, schizophrenia, depression, epilepsy, Tourette's syndrome and in smoking cessation.

Non-competitive inhibition of nAChRs may be responsible for many of the adverse effects attributed to drug therapy. For example, the

impairment of cardiovascular function observed during ketamine anesthesia has been associated with the inhibitory action of ketamine on ganglionic nAChRs. The administration of such drugs as methadone (opioid antagonist) mecamylamine or verapamil (antihypertensive agents) often results in gut motility impairment and constipation, which has been associated with their NCI activity on the $\alpha 3\beta 4$ nAChR.

The pentameric bundle of M2 helices forms the "lumen" (Figures 1-3), the central surface of the narrowest part of the channel, which takes part in channel gating and ion selection. The amino acid residues forming the surface of the lumen are quite conserved across different subunits, and form distinct regions of the channel, or "rings" (see Figure 2 and Table 2). These rings are important for proper function and selectivity of the neuronal nAChRs and are common to all subtypes. An illustration of this importance is the fact that even a single point mutation in this domain can lead to a variety of serious diseases e.g., autosomal dominant nocturnal frontal lobe epilepsy, associated with a serine (S) $\rightarrow$ phenylalanine (F) mutation in the M2 segment of the $\alpha 4$ subunit of nAChR (Steinlein, O. K. Nicotinic acetylcholine receptors and epilepsy. *Curr. Drug Target CNS Neurol. Disord.* **2002**, 1, 443-448.). Therefore, the sequence and structure of the M2 subunits forming the luminal domain are important for understanding disease states associated with nAChRs.

The luminal domain of the ion channel has been identified as a high affinity binding site for a large number of exogenous and endogenous substances in both the open and desensitized state. Many drugs, particularly ionizable amines, can elicit deleterious side effects by binding to the surface of the lumen, sterically plugging the channel and blocking the flux of ions. This mechanism is distinct from the traditional cholinergic mechanism of receptor regulation, and ligands inhibiting the receptor in this way are called non-competitive inhibitors (NCIs) or channel blockers. Noncompetitive action on the neuronal nAChR has been assigned to a large number of marketed drugs and their metabolites

and can be responsible for many toxic side effects of various therapies. For example clinical side effects observed during ketamine anesthesia (i.e., the impairment of the cardiovascular function, etc.) have been associated with the inhibitory action of ketamine on ganglionic nAChRs (Friederich, P.; Dybek, A.; Urban, B. W. Stereospecific interaction of ketamine with nicotinic acetylcholine receptors in human sympathetic ganglion-like SH-SY5Y cells. *Anesth.* **2000**, *93*, 818-24.). Thus, there is a need to develop models to identify ligands that might be NCIs of nAChRs.

The present invention lies in part in a computer system that generates molecular models of ligand-gated neuronal receptors and a method of using the same. The computer system generates a computer-based model of the inner lumen of a ligand-gated ion channel having binding pockets for non-competitive inhibitors. The computer system simulates interaction of structures from chemical libraries or of any desired compound with the generated computer-based model of the ligand-gated ion channel. The simulation can serve to predict and describe the pharmacological importance of the interaction. Thus, the invention constitutes a system for drug discovery and for screening of a drug candidate for unexpected side effects and toxicities.

In an embodiment of the present invention, as shown in Figure 4, the computer system comprises a memory, e.g. disk 105, storing positional data of the atomic coordinates of the transmembrane portion of at least one subunit of a ligand-gated neurotransmitter receptor protein, and a processor 101 generating a molecular model having a three dimensional shape representative of the pore portion of the ligand-gated neurotransmitter receptor based on positional data. During execution of the process for generating the molecular model, it is understood that the positional data would be stored in, for example, RAM 102, or other memory readily accessible by the processor 101.

Table 1

Residue No	1'	2'	3'	4'	5'	6'	7'	8'	9'	10	11	12	13	14	15	16	17	18	19	20	21	22	23
delta [1] SEQ ID NO: 1	E	K	M	S	T	A	I	S	V	L	L	A	G	A	V	F	L	L	L	T	S	G	R
gamma [2] SEQ ID NO: 2	Q	K	C	T	L	S	I	S	V	L	L	A	Q	T	I	F	L	F	L	I	A	Q	K
alpha 1 [3] SEQ ID NO: 3	E	K	M	T	L	S	I	S	V	L	L	S	L	T	V	F	L	L	V	I	V	E	L
alpha 3 [3] SEQ ID NO: 4	E	K	V	T	L	C	I	S	V	L	L	S	L	T	V	F	L	L	V	I	T	E	T
alpha 4 [5] SEQ ID NO: 5	E	K	I	T	L	C	I	S	V	L	L	S	L	T	V	F	L	L	L	I	T	E	I
alpha 5 [8] SEQ ID NO: 6	E	K	I	C	L	C	T	S	V	L	V	S	L	T	V	F	L	L	V	I	E	E	I
alpha 6 [8] SEQ ID NO: 7	E	K	V	T	L	C	I	S	V	L	L	S	L	T	V	F	L	L	V	I	T	E	T
alpha 7 [6] SEQ ID NO: 8	E	K	I	S	L	G	I	T	V	L	L	S	L	T	V	F	M	L	L	V	A	E	I

alpha 9 [8] SEQ ID NO: 9	**E**	K	V	**S**	L	G	V	**T**	I	L	**L**	A	M	T	**V**	F	Q	**L**	M	V	A	**E**	I
alpha 10 [7] SEQ ID NO: 10	**E**	K	V	**S**	L	G	V	**T**	V	L	**L**	A	L	T	**V**	F	Q	**L**	I	L	A	**E**	S
beta 1 [3] SEQ ID NO: 11	**E**	K	M	**G**	L	S	I	**F**	A	L	**L**	T	L	T	**V**	F	L	**L**	L	L	A	**D**	K
beta 2 [4] SEQ ID NO: 12	**E**	K	M	**T**	L	C	I	**S**	V	L	**L**	A	L	T	**V**	F	L	**L**	L	I	S	**K**	I
beta 3 [8] SEQ ID NO: 13	**E**	K	L	**S**	L	S	T	**S**	V	L	**V**	S	L	T	**V**	F	L	**L**	V	I	E	**E**	I
beta 4 [3] SEQ ID NO: 14	**E**	K	M	**T**	L	C	I	**S**	V	L	**L**	A	L	T	**F**	F	L	**L**	L	I	S	**K**	I
epsilon [8] SEQ ID NO: 15	**Q**	K	C	**T**	V	S	I	**N**	V	L	**L**	A	Q	T	**V**	F	L	**F**	F	L	I	**A**	Q

[1] S.J. Opella, F.M. Marassi, et al., *Nat. Struc. Biol.*, 1999, **6**, 374-379.

[2] Hucho, F.; Tsetlin, V.I.; Machold, J. Eur. J. Biochem. 1996, 239, 539-55.

[3] J.C. Webster, M.M. Francis, et al., *Brit. J. Pharmacol.*, 1999, **127**, 1337-1348.

[4] M.W. Francis, R.W. Pazquez, et al., *Mol. Pharmacol.* 2000, **58**, 109-119.

5) O.K. Steinlein, A Magnusson, et al., *Hum. Mol. Genet.*, 1997, **6,** 943-947.

6) E Bertacini, JR Trudell, Protein Eng. 2002, **15**, 443-453.

7) A B Elgoyhen, D E Vetter et al., Proc Natl Acad Sci USA 2001, 98, 3501-6.

8) ENTREZ protein databank at the US National Library of Medicine

The memory, in particular, stores data of the atomic coordinates of at least an α chain and a β chain of a nicotinic acetylcholine receptor. The data of the atomic coordinates can include atomic coordinates of at least one polypeptide having an amino acid sequence selected from the group consisting of the polypeptides shown in Table 1 (SEQ ID NOS: 1-15). The data of the atomic coordinates should include atomic coordinates of the portion of the transmembrane portion of the subunit consisting of at least the amino acid sequence of residues 8 to 19 of SEQ. ID NOS: 1-15.

The processor 101 can generate a molecular model of the luminal domain portion, especially the pore, of a ligand-gated neurotransmitter receptor having a subunit stoichiometry ranging from $(\alpha)_5(\beta)_0$ to $(\alpha)_0(\beta)_5$. For example, the subunit stoichiometry can include$(\alpha)_2(\beta)_3$ useful for modeling the neuronal nAChR regulating cardiovascular and GI actions. The model may be generated with only four helices to model other LGIC families.

Modeling Step:

In generating a molecular model and simulating its interaction with various molecules, the computer system of the present invention first generates a molecular model of the receptor channel based on a template structure determined in an NMR investigation of synthetic channel model (Opella S.J., Marassi F.M., Gesell J.J., Valente A.P., Kim Y., Oblatt-Montal M., Montal M., (1999) Structures of the M2 channel-lining segments from nicotinic acetylcholine and NMDA receptors by NMR spectroscopy. *Nat. Struct. Biol.* 6:374-9). Using this model, the molecular structures of all of the neuronal subtypes of nAChR can be built. All subtypes of nAChR share several common structural arrangements in the luminal domain, which makes it possible to build the model of a particular subtype using a homology modeling approach.

Once a molecular model is generated, the model is refined. A preferred software package for refining the molecular model is the AMBER

molecular modeling package, e.g. AMBER version 7, (D.A. Pearlman, D.A. Case, J.W. Caldwell, W.S. Ross, T.E. Cheatham III, S. De Bolt, D.M. Ferguson, G.L. Seibel and P.A. Kollman, (1995) AMBER, a package of computer programs for applying molecular mechanics, normal mode analysis, molecular dynamics and free energy calculations to simulate the structural and energetic properties of molecules. *Comp. Phys. Comm.* 91, 1-41). The AMBER package contains a set of molecular mechanical force fields for the simulation of biomolecules and a package of molecular simulation programs. In particular, the model is preferably refined using the "SANDER" program (for Simulated Annealing with NMR-Derived Energy Restraints) was used. SANDER is the main program used for molecular dynamics simulations. SANDER allows for NMR refinement based on NOE-derived distance restraints, torsion angle restraints, and penalty functions based on chemical shifts and NOESY volumes.

Once the model has been refined using the SANDER program of AMBER, the final model is evaluated. A preferred software package for evaluating the final model is the PROCHECK package, e.g. version 3.5.4 (Laskowski R A, MacArthur M W, Moss D S & Thornton J M, (1993) PROCHECK: a program to check the stereochemical quality of protein structures. *J. Appl. Cryst.*, 26, 283-291). PROCHECK checks the stereochemical quality of a protein structure, producing a number of PostScript plots analyzing its overall and residue-by-residue geometry.

In order to construct subtype-specific molecular models, the primary structures of the particular subtypes are required. Different subtypes can be found in different region of the human brain and peripheral nervous system and are responsible for specific functions. Subtype-specific models of the nAChR luminal domain can be utilized in designing subtype-specific NCIs.

The procedure of building the luminal model can be easily adopted to constrain models of luminal domain of other subtypes of the nAChR and with some modification to constrain lumen models of other classes of

ligand-gated ion channels. The procedure is basically explained in the modeling step of Example 1. The model of the α3β4-nAChR can serve as the template to constrain other neuronal and muscular subtypes: since those subtypes are very homologous (see Table 1). Only a few residues need to be modified in order to obtain new subtype. The new model after residue modification must be subjected to energy minimization by AMBER procedures described previously and finally should be evaluated using PROCHECK. Elaborated docking procedures can be applied to those models and the entire approach can be used in detailed molecular characterization of the luminal domain of specific subtypes of nAChR and moreover, subtype specific interaction with different classes of NCIs.

More complicated procedures must be applied if one want to obtain a model of the domain formed by other classes of ligand-gated ion channels (GABA, NMDA, 5HT3 etc). First, amino-acid sequence alignment modeling is performed. An example and detailed description of such analysis can be found in the paper by Bertaccini and Trudel [E. Bertaccini and J.R. Trudell, (2002) Predicting the transmembrane secondary structure of ligand-gated ion channels *Protein Eng.* 15, 443-453]. Thus, homologous parts of the ion channel can be found and a new model of transmembrane domain LGIC can be made. For some LGICs, the transmembrane domain is formed by four transmembrane helices instead of five as in the case of nAChR. In such case one of the helices must be removed and the remaining four need to be properly repositioned in order to form the channel structure. Then the model can be relaxed and refined in AMBER procedures and finally evaluated in PROCHECK. In case of such distinct models the docking procedures need be parameterized by initial studies as described in the simulation step of Example 1 below. The values of the size of the grid box, the dielectric constant and the ga_num_evals must be optimized, since the size and environment of the channel would have been changed significantly.

Using the modeling method of the invention, it has been discovered that there are NCI binding sites at the interface between α and β helices of LGICs, especially of nicotinic AchRs. Among modeled candidate NCIs, the compound enters into a small hydrophobic pocket formed by residues 12, 15 and 18 of the transmembrane domains of the receptor subunits (e.g. SEQ ID NOS: 1-15, Table 1). A hydrophobic group of the NCI compound will interact with this portion of the NCI binding site. A polar group (e.g. an amino group) of a putative NCI can interact by hydrogen bonding with surrounding polar residues (e.g. residues 12 and14 of SEQ ID NOS: 1-10).

Simulation step:

After generating the molecular model, the final molecular model is used as a target protein for docking simulation for compounds that may be potential inhibitors. A preferred software package for docking simulation is the AutoDock package, e.g. version 3.5. AutoDock allows docking of a flexible ligand into a rigid structure of the target protein using genetic algorithms as the search method.

A particular genetic algorithm included in the AutoDock package is the Lamarckian genetic algorithm. The Lamarckian genetic algorithm was preferably used with local search in order to improve efficiency. The Lamarckian genetic algorithm works in a reverse order compared to typical genetic algorithms. In particular, new traits in an organism develop because of a need created by the environment and these acquired characteristics are transmitted to its offspring. In AutoDock the ligand's atomic coordinates represent a genotype and fitness is represented by interaction free energy with the proteins. Genotypes are found through interations of the local search and then the atomic coordinates are translated into the ligand's state coordinates as the phenotype. In other words, in AutoDock local search is used to update the fitness associated with an individual in the genetic algorithm selection.

The Lamarckian genetic algorithm uses as input a grid data set produced by the AutoGrid module. The AutoGrid module is used to create

3-dimensional maps over the host protein using several atom specific and electronic probes at each grid point.

Results of these simulations allow the classification of tested compounds in terms of free energy of binding, which leads to the identification of ligands that may be potent inhibitors. The same approach can be used to design new compounds with high affinity binding properties to a specific subtype of the nAChR. A compound that is identified as a non-competitive inhibitor of a LGIC is one having a ΔG less than –6 kcal/mol, preferably less than –7 kcal/mol, still more preferably one having a ΔG less than –10 kcal/mol.

The ligand structures used in docking simulations are preferably made using the HyperChem package (of HyperCube Inc., Gainsville, FL). In particular, it is preferred that the AM1 semiempirical method implemented in HyperChem be used to minimize the system energy and to calculate atomic charges in final structures (J.J.P. Stewart, Semiempirical molecular orbital methods, in: K.B. Lipkowitz, D.B. Boyd (Eds.), *Reviews in Computational Chemistry*, vol. 1, VCH, New York, 1990, pp. 45–81).

The *in silico* approach described above can be supported by examining the NCI-nAChR interaction by affinity chromatography (Jozwiak K, Haginaka J, Moaddel R and Wainer IW (2002) Displacement and nonlinear chromatographic techniques in the investigation of interaction of noncompetitive inhibitors with an immobilized nicotinic acetylcholine receptor liquid chromatographic stationary phase. *Anal Chem* 74: 4618-4624), preferably in an iterative fashion. Chromatographic affinity screening can provide experimental data that is then employed for proper parameterization of the computer-based molecular simulation. Alternatively, the results of computer-based simulation can be related and evaluated by further chromatographic and functional experiments.

Until recently, the screening of drug candidates for activity as NCIs was not a standard procedure in the drug development process. However,

the present invention will permit pharmaceutical companies to rapidly screen their potential drugs for NCI properties. In addition, the luminal domain of nAChR can be used as a target in drug discovery programs, which represents a new therapeutic approach to the treatment of diseases such as Alzheimer's and Parkinson's diseases and for treatment of drug and tobacco dependency, which are related to LGIC functions, especially to nAChR functions.

The nAChR, for example, was found to contain two cholinergic agonist binding sites located at the interface between the α and β subunits and on the extracellular N-terminal of the α subunits. These sites are key targets for drug discovery in a variety of diseases, including Alzheimer's disease ($\alpha_4\beta_2$), Parkinson's disease ($\alpha_3\beta_2$), cardiovascular and GI actions ($\alpha_3\beta_4$), anxiety and depression ($\alpha_4\beta4$), short term memory ($\alpha7$) and auditory function and development ($\alpha9$).

Candidate NCI compounds discovered by the computational modeling method of the invention can be confirmed by *in vitro* experimental methods. Two preferred methods are by binding experiments or by functional assays. Either of these methods may employ the target LGIC, a population of LGICs representing the target receptor and receptors that the compound should preferably not inhibit (to avoid side effects), or a population of LGICs representing a group of target receptors (with or without a group representing LGICs that the compound should preferably not inhibit). The LGICs for the *in vitro* functional assays can be present either as expression products in cells, as partially purified proteins, e.g. membrane preparations made as known in the art, or as isolated proteins. If isolated proteins are used in binding experiments, the proteins are preferably immobilized.

A preferred binding assay is a displacement assay performed as described by Jozwiak et al. [Jozwiak K, Haginaka J, Moaddel R and Wainer IW (2002) Displacement and Nonlinear chromatographic techniques in the investigation of interaction of noncompetitive inhibitors

with an immobilized α3β4 nicotinic acetylcholine receptor liquid chromatographic stationary phase. *Anal Chem* **74**: 4618-4624.] Using this assay, a compound is identified as a non-competitive inhibitor of the ligand-gated neurotransmitter receptor as one that specifically binds to the ligand-gated neurotransmitter receptor with a k' value greater than 8, preferably with a k' value greater than 9 or even more preferably a k' value greater than 10.

Specificity of NCI binding to particular LGICs can be shown by displacement of compounds that are selective for the pore portion of the desired LGIC. Specificity of the binding to a nicotinic AChR and homologous receptors can be shown by displacement by mecamylamine. Displacement of mecamylamine at a concentration of 10 μM (of mecamylamine) indicates good specific binding, ability to displace mecamylamine at a concentration of 40 μM indicates strong specific binding. Preferably it is possible to displace mecamylamine at a concentration of 100 μM. Thus, a compound that is a preferred NCI of a nicotinic AChR is one that exhibits a k' of greater than 8 in a chromatographic binding experiment and can be displaced by mecamylamine at a concentration of 10 to 100 μM.

Preferred functional ion channel activity assays are described by Hernandez et al. [Hernandez SC, Bertolino M, Xiao Y, Pringle KE, Caruso FS and Kellar KJ (2000) Dextromethorphan and its metabolite dextrorphan block α3β4 neuronal nicotinic receptors. J Pharmacol Exp Ther 293: 962-967] and by Jozwiak et al. [K. Jozwiak, SC Hernandez, KJ Kellar, IW Wainer (2003) The Enantioselective Interactions of Dextromethorphan and Levomethorphan with the α3β4-Nicotinic Acetylcholine Receptor: Comparison of Chromatographic and Functional Data submitted to J Pharmacol Exp Ther]. In brief, 1-ml aliquots of cells in growth medium were plated onto 24-well plates coated with poly(D-lysine). The plated cells were grown at 37°C for 16 to 18 h until reaching 90 to 100% confluence. On the day of the experiment, the growth

medium was aspirated and the cells were incubated in fresh medium containing 2 μCi/ml ^{86}RbCl for 4 h at 37°C. After this loading procedure, the medium was aspirated and the cells were washed three times with 1-ml aliquots of buffer (15 mH HEPES, 140 mM NaCl, 2 mM KCl, 1 mM $MgSO_4$, 1.8 mM $CaCl_2$, and 11 mM glucose at pH 7.4) to remove $^{86}Rb^+$ free in the medium. After washing, 1 ml of buffer with or without the drugs under study was added to each well, and the cells were incubated for 2 min. The incubation buffer was then collected, after which the cells were lysed in 0.1 N NaOH. The radioactivity in the buffer samples and cell lysates was measured by liquid scintillation counting. The total $^{86}Rb^+$ loaded into the cells (after washing) was calculated as the sum of the buffer samples and the cell lysates from each well, and the amount of $^{86}Rb^+$ efflux was then expressed as a percentage of the total $^{86}Rb^+$ loaded (fractional release). Stimulated efflux was defined as the difference between efflux in the presence and absence of nicotine (*i.e.*, total minus basal efflux). The maximum $^{86}Rb^+$ efflux, found at a nicotine concentration of ~300 μM or higher, was ~45% of the amount loaded and was independent of the amount of $^{86}Rb^+$ loaded into the cell. In studies to determine the inhibition of nicotine-stimulated $^{86}Rb^+$ efflux by the drugs under study, data were expressed as a percentage of control values measured with 100 μM nicotine.

In these assays a compound is identified as a NCI that inhibits the ion channel activity of the ligand-gated neurotransmitter receptor in nicotine stimulated $^{86}Rb^+$ efflux with an IC_{50} lower than 50 μM. A more preferred NCI compound is one that inhibits ion efflux with an IC_{50} lower than 5 μM. Even more preferable compounds are those that inhibit ion efflux with an IC_{50} lower than 500 nM. One of skill in the art will recognize that compounds that are effective at even lower concentrations are still more preferable, and IC_{50} of 50 nM, or even 5 nM might be observed.

In some instances as described above, it might be preferred to have a NCI that is selective for a particular LGIC. By "selective" is meant that the NCI inhibits the target LGIC with an IC_{50} that is at least 5-fold higher than the IC_{50} of the one or more LGICs that it is desired not to inhibit. The degree of selectivity is preferably 10-fold, more preferably 20- to 50-fold, and still more preferably 100- to 500-fold or more.

On the other hand, the binding assays or functional assays also can be used to provide initial data that can be used to constrain the *in silico* modeling method described above. Alternatively, the *in silico* modeling and the *in vitro* assays can be run iteratively to converge upon NCI compounds that have desired properties.

Methods for synthesis of compounds of the invention are considered within the skill of the ordinary synthetic chemist. Preferred NCI compounds have the above structural features and exhibit activity of inhibiting the ion-channel activity of a ligand-gated neurotransmitter receptor in nicotine stimulated $^{86}Rb^{+}$ efflux with an IC_{50} lower than 100 μM or other activities as set forth in detail above.

Dosage of compounds used for treatment of a subject can be easily determined by the ordinarily-skilled pharmacologist using known pharmacokinetic and pharmacodynamic assays and calculations from IC_{50} data obtained by the inventive method. Doses of from 100 μg to 500 mg per dose are typical. Formulation and administration of compounds useful for treatment is also well-known in the art. For example, many of the compounds listed in Table 2 have been administered therapeutically and it is expected that compounds of the invention can be similarly formulated and administered.

Example 1: Modeling of the Lumen of a α3β4 nAChR and docking of a putative NCI

The molecular model of a δ-M2 - nAChR transmembrane channel determined by frozen state NMR was used as the template for further modification (atomic coordinates were found in Protein Data Bank – PDB id: 1EQ8). This model represents a channel that mimics the transmembrane arrangement of known LGICs (Opella S.J., Marassi F.M., Gesell J.J., Valente A.P., Kim Y., Oblatt-Montal M., Montal M., (1999) Structures of the M2 channel-lining segments from nicotinic acetylcholine and NMDA receptors by NMR spectroscopy. *Nat. Struct. Biol.* 6:374-9). The model channel consisted of 5 uniform polypeptides oriented around a central pore. The amino-acid sequence of this polypeptide is analogous to the sequence of transmembrane M2 segment of δ subunit of nAChR found in *Torpedo californica.*

In the δ-M2 - nAChR transmembrane channel, the spatial arrangement of polypeptide helices conserves five-fold symmetry, with certain residues exposed to the center of the pore. These residues (predominantly polar) form an explicit surface of the channel. This is consistent with the concept of the presence of amino acid rings distributed along the pore and is a common property found in all subtypes of nAChR and also other ligand-gated ion channels [Changeux J.P., Galzi J.L., Devillers-Thiery A., Bertrand D., (1992) The functional architecture of the acetylcholine nicotinic receptor explored by affinity labelling and site-directed mutagenesis. *Q. Rev. Biophys.* 25: 395-432].

With respect to the spatial arrangement of five helices in the luminal domain, distribution of certain amino-acid rings along the channel is a common property of all subtypes of nAChR. Since primary sequences across different subtypes are predominantly homologous as presented in Table 1, and essential (exposed) residues are highly conserved, a subtype specific model of the luminal domain can be built using homology modeling techniques.

Based on the sequence comparison presented in Table 1, the initial model was modified by exchange of δ helix residues into α3 and β4 using the SYBYL 6.8 molecular modeling system (Tripos Inc., 1699 South Hanley Road, St. Louis, Missouri, 63144, USA). Therefore, the channel containing α3, β4, α3, β4 and β4 helices, respectively, was constrained.

The model was further refined by energy minimization using the Sander_Classic module of AMBER 6.0 software. Both termini of each helix were blocked in a standard AMBER procedure: acetyl beginning groups (ACE) and N-methylamine ending group (NME) groups were attached, respectively, to each helix. The AMBER '94 force field (Cornell, W.D., Cieplak, P., Bayly, C.I., Gould, I.R., Merz, Jr. K.M., Ferguson, D.M., Spellmeyer, D.C., Fox, T., Caldwell, J.W., Kollman, P.A., (1995) *J. Am. Chem. Soc.* 117, 5179-5197) parameters were used for energy minimization with the convergence criterion of the root-mean-square of the gradient to be less than 1.0E-4 kcal/mole Å. Each minimization run was started with the steepest descent followed by the conjugate gradient method. A distance-dependent dielectric function was used to evaluate the electrostatic energy. The energy minimization run was carried-out in stages by relaxing i) only hydrogen atoms, ii) hydrogen + side-chain atoms, or iii) all atoms except alpha-carbons. Finally, a restrained minimization was also performed on the alpha-carbons of all the chains/residues of the model. This was to relax the structure but keep it near the initial position of the known template structure (PDB accession no. 1EQ8). Respective scripts used to run model refining with AMBER are presented in Apendix 1.

Using PROCHECK to evaluate the model it was found that the whole luminal domain is constrained fully by α-helix secondary structure. Along the lumen model seven rings of residues exposed to the center of the channel can be found; three polar residues (E, T and S) and then three apolar residues (L, V/F and LL) and the last polar residue (E/K).

It is believed that apolar rings in the middle of the structure form the actual "gate" of the channel and play a role in conformational change of the receptor from a closed to an open state. Polar residues on both sides of the "gate" participate in the cation selective function of the receptor. An important structural parameter found in the obtained model is the change in position from valine in the α3 sequence to phenylalanine in the β4 sequence (see residue 15 in Table 1). This provides the formation of small pockets between α3 and β4 subunits, found during the simulation of NCI-α3β4-nAChR interactions. The developed model of α3β4-nAChR luminal domain can be used as a template to constrain homologous systems of other nicotinic receptors, especially neuronal nicotinic receptors, and other ligand-gated ion channels.

The resulting atomic coordinates represent the final model. Figure 5 illustrates the electrostatic potential of the inner surface of the ion channel, and especially the electronegative potential of the cation selector of the channel. Figure 3c shows an example of the resulting luminal domain model having five helices forming the wall of the ion channel. Figure 3d shows a luminal domain model in perpendicular view with residue rings.

In order to perform docking simulations, the AutoGrid module was first used to create 3-dimensional maps over the host protein using several atom specific and electronic probes at each grid point. An example parameterization file for the AutoGrid module used in this example can be found in Appendix 2. The optimal size of constrained grid maps was a 22.5x22.5x45 Å box (i.e., a grid of 60x60x120 points, each separated by 0.375 Å). This allowed exploration of the whole internal space of the lumen domain but prevented ligands from being bound on the external side. The grid-box size can be altered in the 3rd dimension (along the lumen) in order to explore interaction with a particular segment of the lumen or to calculate the interaction profile along the model.

An important parameter to properly explore electronic interaction in ligand receptor complexes is the dielectric constant value (*d*) used to calculate the electronic grid map. During the initial evaluation tests, the standard distant-dependent dielectric constant did not produce proper results: the electrostatic interaction were almost zero. The simulation did not discriminate between neutral and protonated ligands.

Table 2. ΔG (kcal/mol) of best docked conformation obtained in different dielectric environment.

Diel.const.	Dist. dependent	40	30	20	15	10	5	1
MCM					-6.26			-
MCM +					-	-6.43	-6.76	19.52
	-6.23	-6.22	-6.22	-6.23	11.01	-	-	-
	-6.60	-7.56	-8.13	-9.29		14.47	27.25	138.2
DMT				-8.71	-8.73	-8.81	-8.99	
DMT +	-8.65	-8.66	-8.68	-	-	-	-	
	-8.74	-9.46	-9.77	10.39	11.87	15.72	28.00	
LMT				-8.38	-8.40	-8.49	-8.70	
LMT +	-8.31	-8.33	-8.34	-	-	-	-	
	-8.95	-9.53	-9.81	10.59	12.28	15.69	27.85	

A detailed test of several *d* values was carried out using three pairs of ligands and the results are presented in Table 2. Table 2 shows an unexpected diminished difference between neutral and protonated systems when distant-dependent *d* was used; differences gradually increase with decreasing *d*. Simultaneously the increase in electrostatic impact in the ligand receptor interaction was noticed when a low dielectric

value was used. However, a very low value ($d \leq 10$) produced unrealistic ΔG values. Finally, as a mater of compromising these two effects, $d = 15$ was chosen for final calculations as the value producing suitable electronic properties of the ligand-receptor complex in the transmembrane ion channel system. This approach is in agreement with values of the dielectric constant in transmembrane pores obtained by theoretical calculations (Cheng et al., (1998) *Eur. Biophys J.*, 27 105-112 and Gutman et al., (1992) *Biochim. Biophys Acta* 1109: 141-148) where it was found that the actual dielectric constant in transmembrane channels remains low and ranges from 25 to 5 depending on the structure. Thus, in the case of the NCI-nAChR docking simulations d value can vary from 10 to 20.

The resulting ligand 3D structure was loaded into the AutoDock system and was iteratively sampled over previously created grid-maps in order to find optimal positions and the lowest energy of interaction. An example parameterization file for the AutoDock module used in this example can be found in Appendix 3.

The Lamarckian genetic algorithm with local search was used from the AutoDock package. Atomic coordinate files of ligands were transformed into a format suitable to AutoDock using the HIN2PDBQ script (Johansson M. (2002) Some computational chemistry related python conversion scripts. See Web site helsinki.fi/%7Empjohans/python/).

The ligand structures used in the docking simulations were made using the HyperChem software package. Further, the AM1 semiempirical method implemented in HyperChem was used to minimize the system energy and to calculate atomic charges in final structures.

An initial simulation was performed in order to optimize the docking settings. Since previously described docking space seemed to be large in the model of α3β4-nAChR active site (22,781.25 Å^3) it was important to optimize the maximum number of energy evaluations (ga_num_evals)

required in each search run. It was found that too low a value of ga_num_evals could result in finishing the simulation too quickly, and the global minimum of the complex conformation may not be found. A set of test simulations on several ligands including conformationally flexible and rigid systems was performed. It was found that a ga_num_evals value of at least 5 million is required to assure obtaining a statistically significant number of lowest energy complexes. In the case of bigger ligand molecules with more than 2 rotatable bonds, the optimal value should be at least 50 million. Higher values are acceptable; however higher values may dramatically increase the time of each simulation.

The optimal number of docking search runs was found to be 50. Again the number of docking search runs can be higher, but would take more time for simulation and have no effect on the final result.

AutoDock 3.5 implemented a free-energy scoring function that is based on a linear regression analysis, the AMBER force field, and a large set of diverse protein-ligand complexes with known inhibition constants (e.g. see Web site at scripps.edu/pub/olson-web/doc/autodock/). This function was employed to estimate the free energy change of the NCI-nAChR complex and eventually lead to an estimated inhibition constant of a particular ligand. Docking simulations allow quantitative classification of the stability of the NCI-nAChR complexes formed by tested ligands in terms of free energy of binding, which eventually lead to the identification of ligands exerting potent inhibitory properties. It was found that molecular systems forming the complex with ΔG value lower than –6.0 kcal/mol should be considered as potential NCIs. Lower ΔG values represent more potent NCI compounds. Preferred NCI compounds exhibit a ΔG value lower than –7.0 kcal/mol; more preferred compounds exhibit a ΔG value lower than –10.0 kcal/mol.

Detailed exploration of the spatial arrangement of ligand-receptor conformations leads to building a pharmacophore model of a subtype specific NCI-nAChR. Simulations on the $\alpha 3\beta 4$ model showed that NCIs

bind predominantly in the channel in the apolar domain (F/V ring). Tested structures primarily entered a small hydrophobic pocket formed between α3 and β4 subunits and subsequently interacted with protein side chains, forming hydrogen bonds. It is expected that this is a type of interaction that would not be found in those receptor subtypes that lack the bulky phenylalanine residue in this position. Since there are two quasi-symmetrical pockets between α3 and β4 helices in the model, ligands most likely form two separate clusters on these two symmetrical sites (e.g, Figure 6) at which the energy of interaction does not significantly differ. Estimated free energies of docking are in the range of experimental IC_{50} of tested inhibitors and also can be related to experimental affinity chromatography results. The model can be applied to a variety of compounds and is useful for *in silico* designing of new drugs with particularly high non-competitive inhibitory activity.

Example 2: Chromatographic assay of NCI activity

Chromatographic studies based on immobilized nAChRs were performed to characterize ligand binding for broad groups of compounds. In order to further understand the mechanistic action of NCIs on the molecular level, the model of the transmembrane domain of the α3β4 nAChR was built and used for computer simulations of docking inhibitors into the receptor. The entire approach allowed the classification of NCIs in terms of their functional effectiveness.

Figure 7 presents compounds tested on an α3β4 nAChR column. The chemicals can be divided into several subgroups. The first group contains drugs from different origin, which are well known as non-competitive inhibitors of nAChRs. The second group is of the dextromethorphan family, levomethorphan, dextromethorphan and its analogues, and the final group is verapamil, its congeners, and metabolites. In order to properly assess the influence of non-specific retention, five other chemicals (acetanilide, acetaminophen, 2,4-

dinitrobenzoic acid, 3,4-dimethoxybenzoic acid and phenylbutazone) were tested as negative controls. The affinity of ligands was investigated by non-linear chromatography on an α3β4 nicotinic receptor affinity column.

10^6 Cells from the KXα3β4R2 cell line were suspended in Tris-HCl [50 mM, pH 7.4] (buffer A), homogenized for 30 sec, and centrifuged at 35,000 x g for 10 min at 4 °C. The pellet was resuspended in 2% cholate in buffer A and stirred for 2 h. The mixture was centrifuged at 35,000 x g for 30 min, and the supernatant containing α3β4 nAChR-cholate solution was collected. 200 mg of the IAM stationary phase was added to the α3β4 nAChR-cholate solution. Subsequently the solution was stirred for 1 h. The suspension was dialyzed against 2 x 1L buffer A for 24 h at 4 °C. The IAM liquid chromatographic support containing the α3β4-nAChR was packed into a HR5/2 glass column to form a chromatographic bed of 20 mm x 5 mm i.d. The α3β4-nAChR column was then placed in the chromatographic system and used.

Aqueous solutions [10 μM] of each compound were prepared and 20 μl aliquots were injected into column. The mobile phase was composed of ammonium acetate [10 mM, pH 7.4] modified with methanol in the ratio 85:15 (v/v). The flow rate was 0.2 ml/min and the experiments were carried out at ambient temperature.

DM and LM were monitored in the positive ion mode (ESI+). The compounds were detected using single ion monitoring at m/z = 272 {$[MW+H]^+$ ion}. The chromatograms were recorded and processed using MassLynx v. 3.5. (Micromass).

The non-linear chromatography approach was used to determine kinetics of the NCI-nAChR interaction in affinity chromatography studies.

The mathematical model assumes limited (and a relatively low) number of active sites on the column. Slow association and dissociation of the drug-protein complex are the main cause of band broadening and asymmetry of the peak profile. The chromatographic peak profiles were analyzed using PeakFit v4.11 for Windows Software (SPSS Inc., Chicago,

IL). The mathematical approach used was the non-linear chromatography (NLC) model derived from Impulse Input Solution [Wade J L, Bergold AF and Carr PW (1987) Theoretical description of nonlinear chromatography, with applications to psychochemical measurements in affinity chromatography and implications for preparative-scale separations. *Anal Chem* **59**:1286-1295.] and described by Equation 1 (PeakFit User's Manual, p. 8-25):

$$y = \frac{a_0}{a_3}\left[1-\exp\left(-\frac{a_3}{a_2}\right)\right]\left[\frac{\sqrt{\frac{a_1}{x}}\mathrm{I}_1\left(\frac{2\sqrt{a_1 x}}{a_2}\right)\exp\left(\frac{-x-a_1}{a_2}\right)}{1-\mathrm{T}\left(\frac{a_1}{a_2},\frac{x}{a_2}\right)\left[1-\exp\left(-\frac{a_3}{a_2}\right)\right]}\right] \qquad \text{Eqn. 1}$$

where:

y – intensity of signal,

x – reduced retention time,

$$\mathrm{T}(u,v) = \exp(-v)\int_0^u \exp(-t)\mathrm{I}_0\left(2\sqrt{vt}\right)dt$$

$\mathrm{I}_0(\,)$ and $\mathrm{I}_1(\,)$ are Modified Bessel functions

a_0 - area parameter,

a_1 - center parameter, reveal to true thermodynamic capacity factor,

a_2 - width parameter,

a_3 - distortion parameter.

Experimental chromatograms obtained by single injection of ligand into the chromatographic column with immobilized receptor were processed with PeakFit v4.11 software. After standard linear baseline subtraction, each peak profile was fitted to the NLC function. The set of NLC parameters (a_0, a_1, a_2 and a_3) was collected for each profile and used for the calculation of descriptors of the kinetic interactions with the immobilized nAChR, dissociation rate constant (k_{off}); equilibrium constant (K_a); association rate constant (k_{on}) real thermodynamic capacity factor

(k'), according to the following equations:

$$k' = a_1 \qquad \text{Eqn. 2}$$

$$k_{off} = \frac{1}{a_2 t_0} \qquad \text{Eqn. 3}$$

$$K = \frac{a_3}{C_0} \qquad \text{Eqn. 4}$$

$$k_{on} = k_{off} K \qquad \text{Eqn. 5}$$

where: t_0 is the dead time of a column (time needed by non-retained substance to reach the detector); C_0 is a concentration of solute injected multiplied by a width of the injection pulse (as a fraction of column dead volume).

Thus, by analyzing the ligand in an immobilized receptor system four descriptors can be collected: retention (k'), association rate constant (k_{on}), dissociation rate constant (k_{off}) and equilibrium constant (logK). It was found that ligands which are non-competitive inhibitors have k' greater than 8, k_{on} greater than 10 x 10^{-6} $M^{-1}s^{-1}$ (preferred inhibitors have k_{on} of greater than 15 x 10^{-6} $M^{-1}s^{-1}$ especially potent inhibitors have k_{on} greater than 30 x 10^{-6} $M^{-1}s^{-1}$), k_{off} smaller than 15 s^{-1} (preferably lower than 2 s^{-1}) and logK greater than 5.9 (preferably greater than 6.5).

The k_{on} value obtained in chromatographic experiments is the one which is closely correlated with IC_{50} values from functional *in vitro* or *in vivo* experiments. In the docking simulation, it is preferred that ΔG be lower than –6 kcal/mol (preferably less than –7 kcal/mol, most preferably less than –10 kcal/mol). In functional nicotine stimulated Rb+ efflux experiments, the IC_{50} value is preferrably lower than 100 μM (preferred inhibitors exhibit an IC_{50} < 10 μM).

Table 3. Detailed chromatographic characterization of tested non-competitive inhibitors k' – retention capacity factor, k_{on} and k_{off} are association and dissociation constant rates, respectively (kinetics of

formation and disformation of the complex in chromatographic system), logK is chromatographic equilibrium constant.

5

	$k'_{(NLC)}$	k_{on} [*10^{-6}] [M^{-1}s^{-1}]	k_{off} [s^{-1}]	log K [M^{-1}]
tested drugs				
amantadine	8.98	30.8	6.73	6.66
bupropion	12.97	28.7	5.14	6.75
chlorpromazine	---	---	---	---
clozapine	155.17	24.8	0.55	7.65
dilthiazem	43.53	26.8	1.60	7.22
ketamine	8.25	38.4	8.50	6.65
laudanosine	22.87	25.0	2.18	7.06
mecamylamine	10.89	40.1	5.96	6.83
memantine	16.71	18.8	3.45	6.74
methadone	44.45	15.9	1.37	7.06
methamphetamine	8.38	29.1	6.81	6.63
MK-801	19.10	27.1	3.48	6.89
phenylcyclidine	24.06	23.2	2.69	6.94
quinacrine	---	---	---	---
ethidium	191.82	35.9	0.18	8.30
dextromethorphan	61.30	23.7	1.01	7.37
levomethorphan	35.81	18.6	1.55	7.08
dextrorphan	26.79	20.7	2.30	6.95
3MM	56.47	18.8	1.00	7.28
3OM	26.45	14.3	1.97	6.86
verapamil-R	96.86	31.0	0.68	7.66
verapamil-S	96.32	30.6	0.66	7.66
nor-verapamil-R	97.99	16.0	0.58	7.44
nor-verapamil-S	97.86	15.6	0.61	7.40
galapamil	75.93	20.0	0.74	7.43
D-617	22.22	15.0	2.72	6.74
D-620	17.72	11.6	3.43	6.53
PR-22	99.29	16.0	0.53	7.48
PR-25	19.42	10.6	2.52	6.63
control compounds				
acetaminophen	5.30	8.4	17.17	5.69
acetanilide	5.95	8.2	25.54	5.51
dimethoxybenzoic ac.	4.46	9.8	18.21	5.73
dinitrobenzoic acid	7.77	9.1	12.12	5.87
phenylbutazone	6.29	8.7	22.22	5.59

Values of $\log K$ and k' presented in Table 3 can be regarded as a measure of relative affinity of tested NCI compounds for the nicotinic AChR. Among tested compounds, ethidium, clozapine, verapamil and some of its congeners (PR-22, nor-verapamil and galapamil) have the highest affinities towards the α3β4 nicotinic receptor column as reflected by both $\log K$ and k'. Both verapamil and nor-verapamil were tested for enantioselectivity of binding towards nicotinic affinity column but chromatographic experiments as well as NLC data did not exhibit noticeable differences between enantiomers. Interestingly, dextromethorphan exhibited markedly increased affinity compared to the optical enantiomer levomethorphan.

The NLC approach allows estimating the kinetic rates of the complex formation and dissociation, k_{on} and k_{off}, respectively. The well-known and potent NCIs mecamylamine, ketamine, ethidium and bupropion had high association constant rates. Ketamine, methamphetamine, amantadine and mecamylamine dissociated markedly quicker than other tested ligands. The lowest dissociation constant rates were exhibited by ethidium, clozapine and verapamil congeners.

Table 4. QSAR models build on of chromatographic data

In general, it was found that different molecular properties correlated with chromatographic experimental characteristics: non specific bulkiness (Vol) and lipophilicity ($\log P$; TASA) descriptors, specific shape descriptors (like X_{length}), another group were electronic properties: ability to form hydrogen bonds, E_{HOMO} and N_{order}. Two latter descriptors can be associated with ability of a ligand molecule to protonation. Both bulkiness/shape and Hbond/protonation seem to be important in respect of known mechanism of inhibition by luminal NCIs: ligand must enter the polar pore, interact with negative and polar surface (primarily designated

for cation selection) and eventually block or inhibit the flux of ion during receptor's open stage.

Equation	R	F	n
$\log k' = 5.328(\pm 0.745) + 0.00633(\pm 0.000715)Volume + 0.519(\pm 0.0740)E_{HOMO} -$ $- 0.165(\pm 0.0317)Hbond_{acceptors} - 0.2087(\pm 0.0538)N_{order}$	.961	63.021	26
$\log k_{on} = 4.152(\pm 0.595) + 1.474(\pm 0.483)RASA + 2.383(\pm 0.499)XY_{fract} +$ $+ 0.117(\pm 0.033)N_{order} + 0.0486(\pm 0.0161)Hbond_{acceptors}$	.802	9.441	26
$\log k_{off} = -3.440(\pm 0.653) - 0.00654(\pm 0.000635)Volume - 0.507(\pm 0.0657)E_{HOMO} +$ $+ 0.168(\pm 0.0281)Hbond_{acceptors} + 0.2308(\pm 0.0478)N_{order}$	.969	80.326	26
$\log K = 9.830(\pm 0.752) + 0.00321(\pm 0.000652)TASA + 0.3982(\pm 0.0794)E_{HOMO} -$ $- 0.057(\pm 0.022)X_{length}$	.908	34.654	26

Examples of complexes resulting from simulations are provided in Figures 6, 8 and 9. Figure 6 shows a two cluster interaction of the ligand PCP with α3β4. Figure 8 shows the mecamylamine luminal domain of α3β4. Figure 9 shows the MK-801 luminal domain of α3β4.

Quantitative results of simulated docking affinities were related to experimental results from chromatographic studies. Using AutoDock's scoring function, estimated inhibition constant were calculated. These values exhibited very good correlations with affinity data from NLC calculations (Figure 10). This correlation can be illustrated by equation:

$$\log k' = 0.418(\pm 0.037)\log(1/K_i) - 0.89(\pm 0.19)$$
$$r = 0.930 \quad F = 127.7 \quad n = 22$$

Table 5. the collection of dextromethorphan (DM) / (LM) levomethorphan characterization by different approaches (chromatographic and docking were explained above), *functional in vivo* is nicotine stimulated Rb+ efflux experiments: it was found that DM has significantly longer recovery time than LM, which was predicted by chromatographic and docking modeling. The IC_{50} does not significantly differ.

	Descriptor	DM	LM
functional in vivo	IC_{50} [μM]	10.10(±1.10)	10.90(±1.08)
	% recovery after 7 min. washout	49.83(±5.16)	79.00(±3.50)
	% recovery after 4 h. washout	82.09(±3.64)	94.09(±4.43)
chromatographic (NLC and van't Hoff)	k'	61.30 (±0.27)	35.81(±0.15)
	k_{on} [$\mu M^{-1}sec^{-1}$]	23.66(±0.61)	18.61(±0.38)
	k_{off} [sec^{-1}]	1.01(±0.01)	1.549(±0.002)
	K_a [μM^{-1}]	23.40(±0.36)	12.01(±0.23)
	$\log K_a$	7.37	7.08
	ΔH^o [kcal mol^{-1}]	-6.92(±0.19)	-6.59(±0.18)
	ΔS^o [cal $mol^{-1}T^{-1}$]	-15.70(±0.7)	-15.20(0.6)
	ΔG^o [kcal mol^{-1}]	-2.33(±0.4)	-2.04(±0.4)
docking	ΔG [kcal mol^{-1}]	-8.73	-8.40
	E_{docked} [kcal mol^{-1}]	-8.84	-8.52
	K_i [M]	$3.98*10^{-07}$	$6.91*10^{-07}$
	$\log K_i$	-6.40	-6.16

Enantiomers have identical physiochemical properties and, therefore, all possible non-specific interactions between the enantiomers of a chiral NCI and an immobilized nAChR stationary phase should be equivalent. Any differences in the chromatographic retention between the enantiomers will

be due to specific binding interactions with the active site of the protein. Figure 11 shows chromatograms of dextromethorphan (DM) and its enantiomer – levomethorphan (LM). The pair of enantiomers was further investigated by chromatographic, docking and functional studies (Table 5). It was learned from the chromatographic experiments that the drug dextromethorphan (DM) exert higher affinity on α3β4-nAChR than its enantiomer levomethorphan (LM) and the difference in ΔG of the complexes was 0.3 kcal/mol. These data were valuable in evaluating parameter selection during initial tests of the docking simulations to optimally choose the channel dielectric constant or evaluate the usefulness of the scoring function for calculating estimated ΔG implemented in AutoDock. The docking simulations give insights into chiral recognition on the molecular level (Figure 12). In binding to the α3β4 luminal domain, both molecules interact initially with a hydrophobic pocket on the border between the α3 and β4 helices (Figures 12a). This binding determines the positions of the terminal amine group (blue) differently for dextromethorphan (grey) than levomethorphan (magenta). The amine group of dextromethorphan can easily form secondary interaction hydrogen bonds with neighboring polar residues (orange balls), while levomethorphan is less likely to form such interaction. This makes a difference in stabilities of two complexes by ca. 0.3 kcal/mol determined by both docking and chromatographic analysis (Figure 11).

Furthermore, the estimated inhibition constant obtained during the simulations is very well correlated with equilibrium measures obtained in affinity chromatographic experiments.

Example 3: QSAR – 3D clustering technique

Classical methods for the identification and characterization of non-competitive inhibitors to ligand gated ion channels are time consuming. They are not applicable to the rapid screening of chemical libraries for potential new drug candidates nor can they be routinely used in the new

drug development process. An important advancement in the area is the development of a method of identification of potent NCIs. The method is based of the chemometric processing of the chromatographic data obtained using a stationary phase modified by immobilization of particular subtype of the receptor. The non-linear chromatography approach allows description of the NCI-receptor interactions in terms of real thermodynamic capacity factor (k'), equilibrium constant for binding (K_a) and kinetics rate constants for association (k_a) and dissociation (k_d). We have determined that a strong correlation exists between the drug k_d parameter obtained in affinity chromatography experiments and the relative length of the effect of this drug in functional studies (nicotine stimulated efflux of $^{86}Rb^+$, from cells expressing the target nAChR) (K. Jozwiak, J. Haginaka et al., *Anal. Chem.,* **2002**, *74*, 4618-4624. and K. Jozwiak, S.C. Hernandez et al., J. Chromatogr. B. **2003**, *797*,423-431).

A strong relationship between the chromatographic rate constant and the length of the functional effect was found. However, more than chromatographic affinity has been found necessary to predict the IC_{50} value for NCI activity. The non-linear chromatographic parameters determined in these studies were obtained in a dynamic system but under simplified conditions when compared to a functional assay (i.e. no neurotransmitter stimulation, no transmembrane potential, etc.). Thus, the efficacy of the NCI's expressed as IC_{50} values were not directly correlated with the calculated non-linear chromatographic parameters.

Quantitative Structure-Activity Relationship (QSAR) analysis provided models of the chromatographic affinity (Table 6). Each of the derived equations contains a descriptor related to the electronic properties of the NCI's, E_{HOMO} (Energy of the Highest Occupied Molecular Orbital), TPSA (Total Polar Surface Area) or a number of hydrogen bond acceptors. These models are consistent with the fact that NCI's bind at the internal surface of the nAChR ion channel, which is highly polar and negatively charged. Three of the four equations also contain a shape descriptor

(Shadow-YZ), which is consistent with the fact that the NCI's bind within a defined space on the receptor. Thus, the QSAR analyses describe a chromatographic and, as discussed above, NCI-receptor process where the primary driving force is electrostatic interactions between positively charged ligands and a negatively charged nAChR, which take place in the structurally defined central pore of the receptor.

Table 6. QSAR equation describing affinity chromatography parameters.

$\log k' = 5.255(\pm 0.942) + 0.491(\pm 0.092)E_{HOMO} + 0.0118(\pm 0.0049)YZ$ $r = 0.894,\ s = 0.168,\ F = 27.929,\ n = 17$	Eqn. 1
$\log k_{on} = 7.693(\pm 0.111) - 0.00787(\pm 0.00257)YZ + 0.0700(\pm 0.0237)Hbond_{acceptors} -$ $- 0.00276(\pm 0.00118)TPSA \qquad r = 0.762,\ s = 0.0883,\ F = 5.997,\ n = 17$	Eqn. 2 Outlier: mecamylamine
$\log k_{off} = -3.096(\pm 0.926) - 0.454(\pm 0.090)E_{HOMO} - 0.0128(\pm 0.00471)YZ$ $r = 0.891,\ s = 0.165,\ F = 26.961,\ n = 17$	Eqn. 3
$\log K = 11.412(\pm 0.604) + 0.492(\pm 0.0669)E_{HOMO}$ $r = 0.885,\ s = 0.135,\ F = 54.130,\ n = 17$	Eqn. 4

A 3-dimensional scatterplot of the variables associated with Eqn. 1, i.e. $\log k'$, E_{HOMO} and YZ, suggested that the whole cassette of tested NCI's could be subdivided into three separate clusters, Figure 13.

The parameter k' is derived from chromatographic experiments using the non-linear chromatography approach described by Jozwiak et al. (Jozwiak K, Haginaka J, Moaddel R, Wainer IW. Displacement and nonlinear chromatographic techniques in the investigation of interaction of noncompetitive inhibitors with an immobilized alpha3beta4 nicotinic acetylcholine receptor liquid chromatographic stationary phase. Anal. Chem. 2002 Sep 15;74(18):4618-24) and applied in Example 2 above. E_{HOMO} is given in electron volts (eV) and is the highest occupied molecular orbital energy. E_{HOMO} is an electronic descriptor of the molecule obtained in molecular simulation. In the present Example E_{HOMO} was calculated

using the MOPAC module in Cerius² software (Cerius2 v. 4.8. Accelrys Inc., San Diego, CA). Additional information about the E_{HOMO} parameter can be found in J.M. Goodman, Chemical application of Molecular Modeling, c. Royal Society of Chemistry. 1998. p. 139.

"Shadow YZ" is a surface area projection descriptor – the molecular surface is projected the YZ plane (determined by principal axis of inertia of the molecule) and the shadow is calculated in Å². In the present example, we used the QSAR+ module of Cerius² software (Cerius2 v. 4.8. Accelrys Inc., San Diego, CA). More information about the surface area projection descriptor can be found in Rohrbaugh et al. (Rohrbaugh RH, Jurs PC. Molecular shape and the prediction of high-performance liquid chromatographic retention indexes of polycyclic aromatic hydrocarbons. Anal Chem. 1987 Apr 1;59(7):1048-54).

A cluster analysis based on the three properties was carried out using K-mean clustering method of variables and the results confirm that there are 3 distinct clusters. K-mean clustering is a standard clustering method that determines a user-specified number of clusters with the goal of minimizing within-cluster variability while maximizing between-cluster variability. In the present example, the method was implemented as in Statistica (STATISTICA v. 6.0. Statsoft Inc., Tulsa, OK).

Cluster 1 was formed by four compounds (dilthiazem and methadone verapamil and nor-verapamil) and can be characterized by high values of $\log k'$ and E_{HOMO} and YZ parameters (mean values / range: 1.645 / 1.3 to 2.2 ; -8.93 / -9.2 to –8.6 and 64.5 / 60 to 70, respectively); Cluster 2 included 8 compounds (dextromethorphan analogs, clozapine, laudanosine and phencyclidine) with high values of $\log k'$ and E_{HOMO} but moderate YZ (mean values / range: 1.61 / 1.3 to 2.2; -8.64 / -9.0 to –7.7; and 50.0 / 45 to 60, respectively); and Cluster 3 contained 7 compounds (MK-801, adamantadine, bupropion, ketamine, mecamylamine, memantine, methamphetamine) with low values of $\log k'$, E_{HOMO} and YZ

parameters (mean value / range: 1.06 / 0.9 to 1.3; -9.45 / -9.8 to –9.1 and 37.9 / 25 to 45, respectively).

The analysis segregates the compounds by size and charge, with the smaller, more electronegative compounds appearing in Cluster 3. This division reflects a pharmacological reality since compounds contained in Cluster 3 can rapidly and deeply penetrate the luminal pore of the nAChR producing a high percentage of blockade per concentration of molecules. This would be reflected in lower IC_{50} values.

The IC_{50} values have been established for 4 in Cluster 1, 4 of the 8 in Cluster 2 and 6 of the 8 in Cluster 3 using the Rb^+ efflux assay described above using cell lines expressing the relevant receptor. KXa3b4R2 is a line of human embryonic kidney 293 cells stably transfected with rat neuronal nicotinic acetylcholine receptor (nAChR) α3 and β4 subunit genes. This cell line can be obtained from Dr. Kenneth Kellar – Department of Pharmacology, Georgetown University, Washington, DC. K177 is a line of human embryonic kidney 293 cells stably transfected with human neuronal nicotinic acetylcholine receptor (nAChR) α3 and β4 subunit genes. These cells can be obtained from Dr. Daniel Bertrand, Dept. of Physiology, University of Geneva, Switzerland. SH-SY5Y cells are a human neuroblastoma clonal subline of the neuroepithelioma cell line SK-N-SH from the bone marrow. This cell ine can be obtained from the European Collection of Cell Cultures (ECACC), catalogue no. 94030304. PC-12 Rat adrenal gland pheochromocytoma cells are available from the American Type Culture Collection, ATCC Number CRL-1721. Results are shown in (Table 7).

When these values were considered in relationship to the compounds in Clusters 2 and 3, 3 of the 4 compounds in Cluster 2 had IC_{50} values ≥ 10 μM while 5 of the 6 compounds in Cluster 3 had IC_{50} values ≤ 10 μM.

Table 7. The IC_{50} values of Rb^+ efflux of various compounds.

Ligand	IC_{50}	Cluster Number	Cell line
methadone	1.9 (±0.2)	1	KXα3β4R2
Verapamil	8.1(±1.3)	1	KXα3β4R2
nor-verapamil	2.6(±1.0)	1	KXα3β4R2
Dilthiazem	2.26(±1.0)	1	KXα3β4R2
dextromethorphan	8.9 (±1.1) 10.1 (±1.10)	2	KXα3β4R2 KXα3β4R2
levomethorphan	10.9 (±1.08)	2	KXα3β4R2
dextrorphan	29.6 (±5.7)	2	KXα3β4R2
phencyclidine	7.0 (±1.3) 5.9	2	KXα3β4R2 SH-SY5Y
MK-801	26.6 (±9.6)	3	KXα3β4R2
mecamylamine	1.0 (±0.04)	3	KXα3β4R2
memantine	6.60(±0.92)	3	K177 (α4β2)
amantadine	3.44(±0.67)	3	K177 (α4β2)
Bupropion	1.4	3	SH-SY5Y
Ketamine	5.2 (±0.5) 1.4	3	PC-12 SH-SY5Y

The method of NCI clustering using Equation 1, above, identifies potent NCIs, i.e. those with low IC_{50}. Compounds belonging to cluster 3 are considered as potential NCIs and are expected to be effective in functional tests. Compounds in the cluster 2 are expected to express weaker inhibition properties. The compounds of cluster 1, which consists of large, bulky compounds with strong chromatographic affinity, are also expected to be potent NCIs. Initially, the IC_{50} value of only one of the four compounds in cluster 1 was known, methadone. The cluster analysis

predicted that verapamil, nor-verapamil and diltiazem should be effective NCIs of the α3β4 nAChR and functional studies confirmed this prediction. Functional studies were carried out using a nicotine-stimulated $^{86}Rb^{+}$efflux assay on KXα3β4R2 cell line expressing α3β4 subtype of neuronal nAChR. The studies revealed that the IC_{50} values of dilthiazem, verapamil and nor-verapamil are 2.3 μM, 8.2μM and 2.1 μM respectively. Thus all compounds in cluster 1 are strong inhibitors. The cluster analysis technique is applied in Example 6 below to identify compounds with high potency as NCIs, which was identification was further verified by functional studies of Rb^{+} efflux.

The technique of cluster analysis using Eqn. 1 also suggests that high NCI potency can be attributed to two structurally different groups of compounds. It can be speculated that the two groups of compounds may express their inhibitory properties by two different molecular mechanisms.

Example 4: Investigation of α3β2 nAChR subtype

The α3β4 subtype of the nAChR is extensively characterized, easily accessible in stably transfected cell lines (e.g., KXα3β4R2) and widely tested in functional studies. Moreover, functional studies of this subtype are relatively easy. However, the transmembrane domain of α3β4-subtype has some unique features not found in other subtypes. As previously stated, the general structure of the luminal domain is believed to be fairly well conserved among the subtypes of the nAChRs. However, the M2 transmembrane part of β4 subunit has one critical mutation (phenylalanine (F) in the β4 subunit at position 15 while most other subunits have a valine (V) in this position (Table 1). As a result the nAChRs containing the β4 subunit may display significantly different properties than would other subunit types and may exhibit differences in the interaction of the nAChR channel with NCIs. The introduction of the phenylalanine moieties on the β4 subunits produces small clefts in the

surface of the luminal domain of the channel. These clefts play an important role in in the binding of NCIs, as described further below. The cleft explains the observed enantioselectivity between dextroemthorphan and levomethorphan (Jozwiak, K.; Hernandez, S.C.; Kellar, K.J.; Wainer, I.W. The enantioselective interactions of dextromethorphan and levomethorphan with the α3β4-nicotinic acetylcholine receptor: comparison of chromatographic and functional data. J. Chromatogr. B. **2003**, *797*,423-431).

The clefts are associated with the presence of phenylalanine in β4 M2 domain and will not exist in other, non-β4 subtypes of the nAChR. Interestingly, the results from a chromatographic study which utilize an immobilized α3β2-nAChR column showed enantioselectivity for dextromethorphan and levomethorphan significantly diminished as compared to the immobilized α3β4-nAChR column (Table 7), further supporting the conclusion that the cleft is a feature of β4 subtype receptors that can be important for NCI activity.

Table 7. Comparison of enantioselectivity of DM/LM pair of enantiomers on two different nAChR systems. Experimental data from affinity chromatography – selectivity factor (α)

	α3β4	α3β2
$\alpha = \frac{k'_{DM}}{k'_{LM}}$	1.62	1.03
$\Delta\Delta G^{\circ} = -RT \ln \alpha$	-0.29 kcal/mol	-0.02 kcal/mol

Based on these observations, a molecular model of α3β2 luminal domain was constructed. The main difference in the structure of the β2-type channel is the exchange of phenylalanines from β4 helices for valines associated with β2 helices (See Table 1). A graphic representation of the model is presented in Figures 3a and 3b. Figure 3b. shows the residues forming the surface of the channel. The distribution of the particular rings

along the channel can be easily noticed. The rings are distributed as follows (from top to bottom): extracellular ring, leucine ring, valine ring, leucine ring, serine ring, threonine ring and intermediate ring (consisting of glutamic acid residues) and this is consistent with general considerations. The α3β2 model revealed some important differences when compared with the α3β4 channel. The most important is the lack of clefts formed on the apolar surface of the lumen. The α3β2 model is considered the more general of the two and represents the shape of the channel associated with majority of subtypes of neuronal nAChR, since there is no substantial difference in the sequence of the exposed residues along the channel when compared with other subunits. Only the β4 subunit possesses a significant mutation of Val → Phe in the valine ring. Therefore, the new model of the α3β2 subtype is more homologous to other important subtypes of nAChR than the α3β4 model and should be considered as a general template for detailed studies of other nAChRs and in some perspective other members of the ligand gated ion channel superfamily.

The different structure of the luminal domain of the α3β2 channel produces a profound change in the docking interaction of NCIs. Since there is no apolar cleft on the surface of the channel, the NCI molecules must find alternative interaction in the binding site. The case of special interest are docking simulations: dextromethorphan and levomethorphan. Figures 12a and 12b present the overlaid lowest energy conformations of these two enantiomers docked onto the model of α3β2 luminal domain. Two molecules adopt different orientations compared to docking onto α3β4 model: the ligands binds primarily to the apolar part of the lumen with nitrogen atom interacting with serine ring. However, in contrast to α3β4 docking, there is no defined cavity on the surface and only side interactions are possible which results in the significantly weaker energy of interaction and, what is even more important, the ΔG difference between DM-α3β2-nAChR complex and LM-α3β2-nAChR complex is

significantly diminished when compared to simulations on α3β4-nAChR model (Table 8).

The presence of the hydrophobic cleft in the α3β4 receptor subtype and its absence from the α3β2 subtype presents a target for designing of compounds that are specific for one subtype over the other.

Table 8. Enantiospecificity of dextromethorphan and levomethorphan in docking simulation studies of the α3β4 and α3β2 luminal channels.

	α3β4	α3β2
ΔG_{DM} [kcal/mol]	-8.73	-7.10
ΔG_{LM} [kcal/mol]	-8.40	-6.93
$\Delta\Delta G$ [kcal/mol]	-0.33	-0.17

Example 5: Designing of new NCI molecules

The molecular models, clustering analysis and dynamic chromatographic method of the invention can be used to design molecules that possess enhanced activity as NCIs of nAChRs. The molecular model of the NCI binding site and docking studies provide an understanding of the mechanism of non-competitive inhibition. Using the docking orientations of molecular NCI-nAChR complexes, we have designed modifications of known molecules to more strongly accommodate the active site and as a result obtained new compounds that express stronger NCI activity. Such new molecules are of interest in the pharmaceutical industry as new treatments of disorders associated with nAChR overactivity, e.g., as aids in smoking cessation.

In general, the docking orientation of a putative NCI is such that the molecule occupies a position within the luminal channel and exhibits a ΔG of about –8.5 kcal/mol. The molecule will generally be designed to have molecular contacts with at least one, preferably 2, 3 or 4 of the side chains of the amino acids lining the luminal channel. Molecular contacts

that are useful in providing high binding energies (i.e. negative ΔG), include hydrogen bonds and pi orbital overlaps.

A structure-activity relation for a NCI of a LGIC has been derived using the above-described methods. Thus, a compound having a bulky hydrophobic moiety (e.g., a phenyl or napthyl ring system or other fused aromatic ring system, cyclopentyl or cyclohexyl ring system, a fused ring system including but not limited to bicyclo [2.2.1] heptane, bicyclo [2.2.2] octane, morphinan and dibenzo [1.4] diazepine) and a primary, secondary or tertiary amino group in proximity to (i.e, approximately 5 to 10 Å from, preferably from 5 to 8 Å from, more preferably less than 7 Å from) said hydrophobic moiety. The amino group can be directly bonded to the bulky hydrophobic moiety or can be linked by a spacer moiety, such as, but not limited to, a short hydrocarbon chain. The amino group can be substituted (-NR_1R_2, where R_1 and R_2 are the same or different and are selected from the group consisting of H, C_1-C_3 alkyl, C_1-C_4 alkoxy, dialkyl keto) . The substituent is preferably one that retains a hydrogen-bonding potential; a preferred substituent is a keto- group, for example a dialkyl keto group, especially $CH_2(C=O)CH_3$. Another preferred substituent is a hydroxyl or alkoxyl (-CH_2OH) group, e.g. a C_1 – C_4 normal or branched alkoxyl group. Preferred substituted amino groups are a dialkyl keto amino group (e.g., $HNCH_2(C=O)CH_3$), a hydroxyl amino group or a methoxy amino group. An example of such a compound is 3-methoxy-17-propane-2-one 9 α, 13α, 14α morphinan.

A preferred compound designed using the method of the above considerations is one comprising a hydrophobic group. A preferred hydrophobic group comprises at least one ring that includes at least two conjugated unsaturated bonds, said ring optionally being fused to additional rings to form a ring system and said additional rings optionally including one or more hetero atoms. Alternatively, the hydrophobic group can be a hydrocarbon chain or saturated cyclic compound. The hydrocarbon chain can be linear or branched and preferably contains

from 4 to 10 carbon atoms, more preferably from 4 to 7 carbon atoms. The hydrocarbon chain can further include alkenyl or alkynl unsaturations at one or two positions.

The compound will also preferably contain a hydrogen bond accepting group, which more preferably is selected from the group consisting of a keto group, a nitrogen-containing heterocyclic group and a guanidinium group. Typically, the ring or ring system and said hydrogen bond accepting group are joined by a linker comprising 1 to 4 carbon atoms and optionally containing an oxygen or sulfur atom.

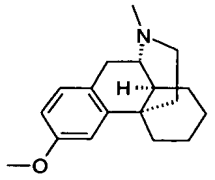
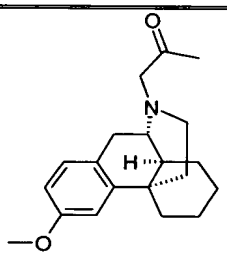
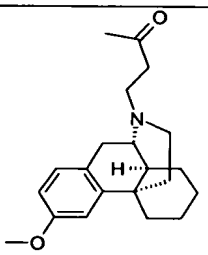
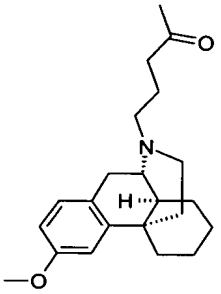
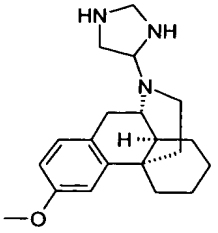
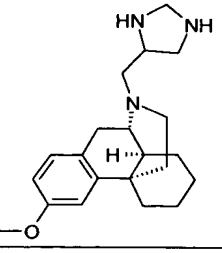
One consideration for design of effective NCI molecules is that the molecule will preferably span portion of the luminal domain from the hydrophobic region defined by the leucine and/or valine rings to the more polar region defined by the serine and/or threonine rings (Figure 2).

The compound will preferably have activity as a non-competitive inhibitor of Rb^+ efflux of a ligand-gated neurotransmitter ion channel receptor with an IC_{50} of less than 10 μM.

As an example of such an approach, we undertook modifications of dextromethorphan (DM). DM possesses strong activity as a NCIs (IC_{50}=10 μM on α3β4-nAChR with a greatly prolonged duration of the NCI action), it easily passes blood-brain barrier and unlike as its enantiomer levomethorphan expresses little action on opioid receptors. The docking orientation of the DM-α3β4-nAChR complex is presented in Figure 15. The molecule occupies the valine/phenylalanine cleft on the border between α3-M2 helix and β4-M2 helix with an amino- group exposed for interaction with polar residues below this cleft. The interaction would be even stronger if the amino group could interact with the serine residues forming the serine ring, but this interaction is prevented by the distance of ca. 5 Å separating two moieties. Study of the complex showed that the energy of interaction should be significantly enhanced if a methyl group attached to nitrogen would be exchanged into a longer moiety with hydrogen bond acceptors in order to allow forming strong hydrogen bonds

and therefore stabilizing the complex. Several possible patterns of dextromethorphan modification were designed and these are shown in Table 9. Those molecules are based on the interaction with α3β4-nAChR and may be possibly selective blockers for this subtype. Compound DM-01 was synthesized and tested for activity in a Rb^+ efflux assay. The synthesis of DM-01 is described in Figure 14 and the data are presented in Figure 15.

Table 9. Molecules designed to inhibit α3β4-nAChR followed by ΔG values obtained in docking simulations (reference ΔG of dextromethorphan = -8.73 kcal/mol).

Compound	Formula	ΔG
dextrometorphan		-8.73 kcal/mol
DM-01		-9.09 kcal/mol
DM-02		-9.35 kcal/mol
DM-03		-10.31 kcal/mol
DM-04		-9.39 kcal/mol
DM-05		-10.18 kcal/mol

Example 6: Prediction of Side Effects of Compounds Mediated by Non-Competitive Inhibition of Ligand-Gated Ion Channels

The analytic methods of the present invention can also be applied to assessment of NCI activity of compounds compounds, both known drugs and novel compounds, to predict side effects. For example, the drugs verapamil, nor-verapamil and dilthiazem are commonly administered for treatment of high blood pressure. An undesirable side effect of these drugs is constipation.

As explained above, the α3β4 nAChR subtype plays a role in regulation of gut motility and the side effects of verapamil, nor-verapamil and dilthiazem on gut motility have been related to NCI activity of these compounds against the nAChR. As an example of application of the analytic methods of the present invention to the investigation of drug side effects, we applied the cluster analysis method to predict the NCI activity of various compounds used as calcium channel blockers for treatment of high blood pressure, or their metabolites (MA – M6 and D-620) and listed in Table 10. NCI activity is predicted if the compound falls into Cluster 1. Predicted NCI activity (or lack thereof) was then confirmed using the Rb^+ efflux assay. Results are shown in Table 10.

The ranges defining clusters are as above and are: Cluster 1 (low IC_{50} values) $\log k'$ from 1.3 to 2.2 and E_{HOMO} from -9.2 to –8.6 and YZ from 60 to 70; Cluster 2 (high IC_{50} values) $\log k'$ from 1.3 to 2.2 and E_{HOMO} from –9.0 to –7.7 and YZ from 60 to 45 ; and Cluster 3 (low IC_{50} values) $\log k'$ from 0.9 to 1.3; E_{HOMO} from –9.8 to –9.1 and YZ from 45 to 25.

The chromatographic method using α3β4 nAChR column was used to obtain experimental affinity for 13 structures (diltiazem and 5 of its metabolites; verapamil and 3 of its metabolites; nicardapine, nifedipine and amlodipine). The computational method of the invention was use to calculate E_{HOMO} and YZ descriptors and the data are presented in Table 10. Based on this data all compounds were assigned to respective clusters (Table 10).

After the prediction has been done based on clustering the actual values of IC_{50} were determined using the nicotine-stimulated $^{86}Rb^{+}$ efflux assay on cell line KXα3β4R2. These data are also presented in Table 10 and the comparison of cluster method prediction with actual activity gives very good agreement – all tested ligands falls into proper categories.

As it can be seen from Table 10 all of the tested compounds could be assigned to either cluster 1 or to cluster 2, which segregate them into two groups: very effective NCIs (IC_{50} < 10 μM – cluster No. 1) and less effective NCIs (IC_{50} > 10 μM – cluster No. 2). The cluster analysis properly predicted the NCI activity of all 13 drugs and metabolites. Furthermore, the results suggest that the cardiovascular benefit attributed to calcium channel blocking activity may derive at least in part from previously unrecognized activity of inhibition of ligand-gated ion channels.

Table 10. Results of the cluster analysis characterization of tested calcium channel blockers.

Ligand	log*k'*	E_{HOMO}	YZ	Cluster No.	IC_{50} [μM]
Dilthiazem	1.64	-8.66306	62.29732	1	2.2
MA	1.61	-8.6465	66.535	1	4.2
M1	1.6	-8.5788	62.40288	2	30.4
M2	1.61	-8.58	57.4339	2	77.6
M4	1.45	-8.4067	61.84228	2	73.2
M6	1.48	-8.6465	58.1142	2	63.1
verapamil	1.99	-9.05746	64.80137	1	8.1
Nor-verapamil	1.99	-9.12446	64.82286	1	2.6
galapamil	1.88	-9.04879	66.25418	1	6.4
D-620	1.25	-9.34918	48.52653	2	48.9
nicardapine	2.33	-8.8397	65.20084	1	2.5
amlodipine	2	-8.7228	62.93348	1	5.8
nifedipine	1.27	-8.6323	58.42415	2	24.7

Compounds named in Table 3, Table 7 or Table 10, or specifically named in Figure 9 or Figure 13, and bupropion, ketamine, laudanosine, mecamylamine, methadone, MK-801, phenylcylclidine, ethidium, and

dextromethorphan are compounds known in the prior art and so are not considered to be inventive compounds *per se* within the scope of the present invention. Methods of the invention for non-competitively inhibiting a LGIC, especially a nicotinic AChR, or for treatment of a disease mediated by overactivity of a nicotinic AChR, exclude the use of bupropion, ketamine, laudanosine, mecamylamine, methadone, MK-801, phenylcylclidine, ethidium, and dextromethorphan.

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

All patent and literature references cited herein are hereby incorporated by reference in their entirety and for all purposes, including the following references:

1. Wainer IW, Zhang Y, Xiao Y, Kellar KJ (1999) Liquid chromatographic studies with immobilized neuronal nicotinic acetylcholine receptor stationary phases: effects of receptor subtypes, pH and ionic strength on drug-receptor interactions. *J Chromatogr B Biomed Sci Appl* **724**:65-72.
2. Zhang Y, Xiao Y, Kellar KJ, Wainer IW (1998) Immobilized nicotinic receptor stationary phase for on-line liquid chromatographic determination of drug-receptor affinities. *Anal Biochem* **264**:22-5.
3. Barrantes FJ. (2002) Lipid matters: nicotinic acetylcholine receptor-lipid interactions (Review). *Mol Membr Biol* **19**:277-84.
4. Morris GM, Goodsell DS, Halliday RS, et al. (1998) Automated docking using a Lamarckian genetic algorithm and empirical binding free energy function. **19**:1639-62.

Appendix 1 AMBER Scripts for stepwise refining the model

All Runs were made in AMBER 6.0. The computer used was SGI Octane.

SGI Octane information is given below:

---

1 195 MHZ IP30 Processor
CPU: MIPS R10000 Processor Chip Revision: 2.7
FPU: MIPS R10010 Floating Point Chip Revision: 0.0
Main memory size: 1536 Mbytes
Xbow ASIC: Revision 1.3
Instruction cache size: 32 Kbytes
Data cache size: 32 Kbytes
Secondary unified instruction/data cache size: 1 Mbyte
Integral SCSI controller 0: Version QL1040B (rev. 2), single ended
Disk drive: unit 1 on SCSI controller 0
Disk drive: unit 2 on SCSI controller 0
Integral SCSI controller 1: Version QL1040B (rev. 2), single ended
IOC3 serial port: tty1
IOC3 serial port: tty2
IOC3 parallel port: plp1
Graphics board: SI
Integral Fast Ethernet: ef0, version 1, pci 2
Iris Audio Processor: version RAD revision 12.0, number 1

The Amber runs were made on a potassium channel receptor model that was built using the template structure of PDB entry 1EQ8 on Sybyl 6.8. Amber 6.0 was used to refine the structure that was built in sybyl 6.8. Scripts used to do the energy minimization are attached below:

#++

SCRIPT 1

#---

#Script for running Sander_Classic in AMBER 6.0
#Relaxing only Hydrogen atoms ----Ravi (May 23, 2002)
#
#
#ALL Hs are relaxed IBELLY OPTION, \epsilon(r)

```
#-------------------------------------------------
 &cntrl
 timlim=36000.,  imin=1, nmropt=0,

 ntx=1,  irest=0, ntrx=1,

 ntxo=1,  ntpr=10, ntwr=0, ntwx=50, ntwv=0, ntwe=50, ntwxm=0, ntwvm=0, ntwem=0,
 ioutfm=0, ntwprt=0,

 ntf=1, ntb=0, idiel=0, dielc=4.0, cut=9.0, ntnb=1, nsnb=25,
 ntid=0, scnb=2.0,scee=1.2, cut2nd=0.0

 ichdna=0,
 isftrp=0, rwell=0.0,
 ipol=0,
 ibelly=1, ntr=0,

 maxcyc=5000, ncyc=550, ntmin=1,  dx0=0.01, dxm=0.05,

 &end
GROUP NUMBER 1
FIND
 * H  * *
 * H1 * *
 * HC * *
 * HP * *
 * HO * *
 * HA * *
 * HS * *
SEARCH
RES 1 125
END
END

#++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
```

SCRIPT 2

```
#-------------------------------------------------
#Script for running Sander_Classic in AMBER 6.0
#Relaxing Hydrogen + Side-Chains ----Ravi (May 23, 2002)
#
#
```

```
#-----------------------------------------------------

# Channel ALL H+SC are moving
#
 &cntrl
 timlim=36000.,  imin=1, nmropt=0,

 ntx=1,  irest=0, ntrx=1,

 ntxo=1,  ntpr=5, ntwr=0, ntwx=50, ntwv=0, ntwe=50, ntwxm=0, ntwvm=0, ntwem=0,
 ioutfm=0, ntwprt=0,

 ntf=1, ntb=0, idiel=0, dielc=4.0, cut=9.0, ntnb=1, nsnb=25,
 ntid=0, scnb=2.0,scee=1.2, cut2nd=0.0

 ichdna=0,
 isftrp=0, rwell=0.0,
 ipol=0,
 ibelly=1, ntr=0,

 maxcyc=5000, ncyc=250, ntmin=1,  dx0=0.01, dxm=0.05,

 &end
GROUP NUMBER 1
FIND
* CT 3 *
* CA B *
* CA S *
* OH S *
* SH S *
* S  S *
* C  B *
* N3 3 *
* *  E *
SEARCH
RES 1 125
END
END
#++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
```

SCRIPT 3:

```
#-----------------------------------------------------
```

```
#Script for running Sander_Classic in AMBER 6.0
#Relaxing everything except alpha-Carbons
#----Ravi (May 23, 2002)
#
#
#-------------------------------------------------------
# Except Alpha C, all other atoms move
#
 &cntrl
 timlim=36000.,  imin=1, nmropt=0,

 ntx=1,  irest=0, ntrx=1,

 ntxo=1,  ntpr=5, ntwr=0, ntwx=50, ntwv=0, ntwe=50, ntwxm=0, ntwvm=0, ntwem=0,
 ioutfm=0, ntwprt=0,

 ntf=1, ntb=0, idiel=0, dielc=4.0, cut=9.0, ntnb=1, nsnb=25,
 ntid=0, scnb=2.0,scee=1.2, cut2nd=0.0

 ichdna=0,
 isftrp=0, rwell=0.0,
 ipol=0,
 ibelly=1, ntr=0,

 maxcyc=5000, ncyc=250, ntmin=1,  dx0=0.01, dxm=0.05,

 &end
GROUP NUMBER 1
FIND
* * 3 *
* * B *
* * S *
* * E *
N N M *
C C M *
CH3 CT M *
* HC M *
SEARCH
RES 1 125
END
END
```

```
#+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
```

SCRIPT 4:

```
#-----------------------------------------------------
#Script for running Sander_Classic in AMBER 6.0
#Restrained minimization of the alpha-Carbons of the channel
#----Ravi (May 23, 2002)
#
#
#-----------------------------------------------------
# Restrained minimization of the alpha-Carbons
#
 &cntrl
 timlim=36000.,  imin=1, nmropt=0,

 ntx=1,  irest=0, ntrx=1,

 ntxo=1,  ntpr=5, ntwr=0, ntwx=50, ntwv=0, ntwe=50, ntwxm=0, ntwvm=0, ntwem=0,
 ioutfm=0, ntwprt=0,

 ntf=1, ntb=0, idiel=0, dielc=4.0, cut=9.0, ntnb=1, nsnb=25,
 ntid=0, scnb=2.0,scee=1.2, cut2nd=0.0

 ichdna=0,
 isftrp=0, rwell=0.0,
 ipol=0,
 ibelly=0, ntr=1,

 maxcyc=2000, ncyc=250, ntmin=1,  dx0=0.01, dxm=0.05,

 &end
GROUP NUMBER 1
10.0
FIND
CA * * *
SEARCH
RES 1 125
END
END
```

```
#+++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++++
```

Appendix 2 AutoGrid Parameter File

```
receptor M3.pdbqs                # macromolecule model
gridfld M3.maps.fld              # grid_data_file
npts 60 60 120                   # num.grid points in xyz
spacing 0.375                    # spacing(A)
gridcenter 0.009 0.026 -0.172    # xyz-coordinates or auto
types CANOH                      # atom type names
smooth 0.5                       # store minimum energy w/in rad(A)
map M3.C.map                     # atom-specific affinity map
nbp_r_eps  4.00 0.0222750 12  6  # C-C lj
nbp_r_eps  3.75 0.0230026 12  6  # C-N lj
nbp_r_eps  3.60 0.0257202 12  6  # C-O lj
nbp_r_eps  4.00 0.0257202 12  6  # C-S lj
nbp_r_eps  3.00 0.0081378 12  6  # C-H lj
nbp_r_eps  3.00 0.0081378 12  6  # C-H lj
nbp_r_eps  3.00 0.0081378 12  6  # C-H lj
sol_par  12.77 0.6844    # C atomic fragmental volume, solvation parameters
constant  0.000     # C grid map constant energy
map M3.A.map                     # atom-specific affinity map
nbp_r_eps  4.00 0.0222750 12  6  # A-C lj
nbp_r_eps  3.75 0.0230026 12  6  # A-N lj
nbp_r_eps  3.60 0.0257202 12  6  # A-O lj
nbp_r_eps  4.00 0.0257202 12  6  # A-S lj
nbp_r_eps  3.00 0.0081378 12  6  # A-H lj
nbp_r_eps  3.00 0.0081378 12  6  # A-H lj
nbp_r_eps  3.00 0.0081378 12  6  # A-H lj
sol_par  10.80 0.1027    # A atomic fragmental volume, solvation parameters
constant  0.000     # A grid map constant energy
map M3.N.map                     # atom-specific affinity map
nbp_r_eps  3.75 0.0230026 12  6  # N-C lj
nbp_r_eps  3.50 0.0237600 12  6  # N-N lj
nbp_r_eps  3.35 0.0265667 12  6  # N-O lj
nbp_r_eps  3.75 0.0265667 12  6  # N-S lj
nbp_r_eps  1.90 0.3280000 12 10  # N-H hb
nbp_r_eps  1.90 0.3280000 12 10  # N-H hb
nbp_r_eps  1.90 0.3280000 12 10  # N-H hb
sol_par   0.00 0.0000    # N atomic fragmental volume, solvation parameters
constant  0.000     # N grid map constant energy
map M3.O.map                     # atom-specific affinity map
```

```
nbp_r_eps  3.60 0.0257202 12  6   # O-C lj
nbp_r_eps  3.35 0.0265667 12  6   # O-N lj
nbp_r_eps  3.20 0.0297000 12  6   # O-O lj
nbp_r_eps  3.60 0.0297000 12  6   # O-S lj
nbp_r_eps  1.90 0.3280000 12 10   # O-H hb
nbp_r_eps  1.90 0.3280000 12 10   # O-H hb
nbp_r_eps  1.90 0.3280000 12 10   # O-H hb
sol_par   0.00 0.0000    # O atomic fragmental volume, solvation parameters
constant  0.236      # O grid map constant energy
map M3.H.map                    # atom-specific affinity map
nbp_r_eps  3.00 0.0081378 12  6   # H-C lj
nbp_r_eps  1.90 0.3280000 12 10   # H-N hb
nbp_r_eps  1.90 0.3280000 12 10   # H-O hb
nbp_r_eps  3.00 0.0093852 12  6   # H-S lj
nbp_r_eps  2.00 0.0029700 12  6   # H-H lj
nbp_r_eps  2.00 0.0029700 12  6   # H-H lj
nbp_r_eps  2.00 0.0029700 12  6   # H-H lj
sol_par   0.00 0.0000    # H atomic fragmental volume, solvation parameters
constant  0.118      # H grid map constant energy
elecmap M3.e.map                  # electrostatic potential map
dielectric 15.0                 # <0, distance-dep.diel;>0, constant
fmap M3.f.map                     # floating point potential gridmap
```

Appendix 3 AutoDock Parameter File

```
seed pid time                   # seeds for random generator
types CANOH                       # atom type names
fld M3.maps.fld                  # grid_data_file
map M3.C.map                      # atom-specific affinity map
map M3.A.map                      # atom-specific affinity map
map M3.N.map                      # atom-specific affinity map
map M3.O.map                      # atom-specific affinity map
map M3.H.map                      # atom-specific affinity map
map M3.e.map                     # electrostatics map
move DMT.out.pdbq                   # small molecule
about -0.088 0.126 0.069           # small molecule center
tran0 random                    # initial coordinates/A or random
quat0 random                     # initial quaternion
ndihe 1                       # number of active torsions
dihe0 random                      # initial dihedrals (relative) or random
tstep 2.0                     # translation step/A
```

```
qstep 50.0                    # quaternion step/deg
dstep 50.0                    # torsion step/deg
torsdof 1 0.3113              # torsional degrees of freedom and coeffiecent
intnbp_r_eps 4.00 0.0222750 12 6   # C-C lj
intnbp_r_eps 4.00 0.0222750 12 6   # C-A lj
intnbp_r_eps 3.75 0.0230026 12 6   # C-N lj
intnbp_r_eps 3.60 0.0257202 12 6   # C-O lj
intnbp_r_eps 3.00 0.0081378 12 6   # C-H lj
intnbp_r_eps 4.00 0.0222750 12 6   # A-A lj
intnbp_r_eps 3.75 0.0230026 12 6   # A-N lj
intnbp_r_eps 3.60 0.0257202 12 6   # A-O lj
intnbp_r_eps 3.00 0.0081378 12 6   # A-H lj
intnbp_r_eps 3.50 0.0237600 12 6   # N-N lj
intnbp_r_eps 3.35 0.0265667 12 6   # N-O lj
intnbp_r_eps 2.75 0.0084051 12 6   # N-H lj
intnbp_r_eps 3.20 0.0297000 12 6   # O-O lj
intnbp_r_eps 2.60 0.0093852 12 6   # O-H lj
intnbp_r_eps 2.00 0.0029700 12 6   # H-H lj
outlev 1                      # diagnostic output level
rmstol 0.5                    # cluster_tolerance/A
extnrg 1000.0                 # external grid energy
e0max 0.0 10000               # max initial ernergy; max number of retries
ga_pop_size 50                # number of individuals in population
ga_num_evals 5000000          # maximum number of energy evaluations
ga_num_generations 27000      # maximum number of generations
ga_elitism 1                  # number of top individuals to survive to next generation
ga_mutation_rate 0.02         # rate of gene mutation
ga_crossover_rate 0.8         # rate of crossover
ga_window_size 10             #
ga_cauchy_alpha 0.0           # Alpha parameter of Cauchy distribution
ga_cauchy_beta 1.0            # Beta parameter Cauchy distribution
set_ga                        # set the above parameters for GA or LGA
sw_max_its 300                # iterations of Solis & Wets local search
sw_max_succ 4                 # consecutive successes before changing rho
sw_max_fail 4                 # consecutive failures before changing rho
sw_rho 1.0                    # size of local search space to sample
sw_lb_rho 0.01                # lower bound on rho
ls_search_freq 0.06           # probability of performing local search on individual
set_psw1                      # set the above pseudo-Solis & Wets parameters
ga_run 50                     # do this many hybrid GA-LS runs
analysis                      # perform a ranked cluster analysis
```

Appendix 4: Atomic Coordinates of the Luminal Channel of a **α3β4 nAChR** Ion Channel

pdb file of the α3β4 nAChR model

ATOM	1	CA	ACE	1	9.270	5.413	-18.665	0.00	0.00
ATOM	2	C	ACE	1	9.064	4.649	-17.364	0.00	0.00
ATOM	3	O	ACE	1	9.286	5.198	-16.285	0.00	0.00
ATOM	4	N	GLU	2	8.656	3.377	-17.484	0.00	0.00
ATOM	5	H	GLU	2	8.496	3.014	-18.412	0.00	0.00
ATOM	6	CA	GLU	2	8.345	2.482	-16.365	0.00	0.00
ATOM	7	CB	GLU	2	7.781	1.164	-16.930	0.00	0.00
ATOM	8	CG	GLU	2	7.274	0.164	-15.874	0.00	0.00
ATOM	9	CD	GLU	2	6.311	0.782	-14.852	0.00	0.00
ATOM	10	OE1	GLU	2	6.525	0.540	-13.643	0.00	0.00
ATOM	11	OE2	GLU	2	5.381	1.495	-15.291	0.00	0.00
ATOM	12	C	GLU	2	9.541	2.246	-15.422	0.00	0.00
ATOM	13	O	GLU	2	9.344	1.832	-14.284	0.00	0.00
ATOM	14	N	LYS	3	10.771	2.539	-15.863	0.00	0.00
ATOM	15	H	LYS	3	10.867	2.901	-16.800	0.00	0.00
ATOM	16	CA	LYS	3	11.990	2.351	-15.083	0.00	0.00
ATOM	17	CB	LYS	3	13.218	2.415	-16.010	0.00	0.00
ATOM	18	CG	LYS	3	13.496	1.120	-16.797	0.00	0.00
ATOM	19	CD	LYS	3	12.434	0.760	-17.851	0.00	0.00
ATOM	20	CE	LYS	3	12.843	-0.456	-18.690	0.00	0.00
ATOM	21	NZ	LYS	3	13.984	-0.166	-19.580	0.00	0.00
ATOM	22	HZ1	LYS	3	14.784	0.109	-19.027	0.00	0.00
ATOM	23	HZ2	LYS	3	14.216	-0.990	-20.116	0.00	0.00
ATOM	24	HZ3	LYS	3	13.741	0.585	-20.211	0.00	0.00
ATOM	25	C	LYS	3	12.132	3.373	-13.949	0.00	0.00
ATOM	26	O	LYS	3	12.566	3.010	-12.857	0.00	0.00
ATOM	27	N	VAL	4	11.753	4.634	-14.194	0.00	0.00
ATOM	28	H	VAL	4	11.400	4.864	-15.112	0.00	0.00
ATOM	29	CA	VAL	4	11.662	5.664	-13.159	0.00	0.00
ATOM	30	CB	VAL	4	11.627	7.065	-13.814	0.00	0.00
ATOM	31	CG1	VAL	4	11.499	8.186	-12.768	0.00	0.00
ATOM	32	CG2	VAL	4	12.901	7.325	-14.639	0.00	0.00
ATOM	33	C	VAL	4	10.413	5.416	-12.307	0.00	0.00
ATOM	34	O	VAL	4	10.455	5.677	-11.110	0.00	0.00
ATOM	35	N	THR	5	9.329	4.884	-12.897	0.00	0.00
ATOM	36	H	THR	5	9.350	4.704	-13.891	0.00	0.00
ATOM	37	CA	THR	5	8.083	4.583	-12.195	0.00	0.00
ATOM	38	CB	THR	5	6.994	4.125	-13.184	0.00	0.00
ATOM	39	CG2	THR	5	5.633	3.934	-12.505	0.00	0.00
ATOM	40	OG1	THR	5	6.830	5.082	-14.210	0.00	0.00
ATOM	41	HG1	THR	5	6.121	4.783	-14.784	0.00	0.00
ATOM	42	C	THR	5	8.300	3.535	-11.096	0.00	0.00
ATOM	43	O	THR	5	7.868	3.747	-9.963	0.00	0.00
ATOM	44	N	LEU	6	8.984	2.425	-11.414	0.00	0.00
ATOM	45	H	LEU	6	9.287	2.286	-12.369	0.00	0.00
ATOM	46	CA	LEU	6	9.311	1.394	-10.436	0.00	0.00
ATOM	47	CB	LEU	6	9.642	0.056	-11.127	0.00	0.00
ATOM	48	CG	LEU	6	10.932	-0.001	-11.976	0.00	0.00
ATOM	49	CD1	LEU	6	12.185	-0.332	-11.150	0.00	0.00
ATOM	50	CD2	LEU	6	10.789	-1.070	-13.070	0.00	0.00
ATOM	51	C	LEU	6	10.367	1.852	-9.428	0.00	0.00
ATOM	52	O	LEU	6	10.366	1.351	-8.308	0.00	0.00
ATOM	53	N	CYS	7	11.216	2.830	-9.782	0.00	0.00
ATOM	54	H	CYS	7	11.170	3.204	-10.719	0.00	0.00
ATOM	55	CA	CYS	7	12.155	3.443	-8.852	0.00	0.00
ATOM	56	CB	CYS	7	13.169	4.290	-9.630	0.00	0.00
ATOM	57	SG	CYS	7	14.449	4.908	-8.504	0.00	0.00

ATOM	58	HG	CYS	7	15.153	5.565	-9.430	0.00	0.00
ATOM	59	C	CYS	7	11.403	4.271	-7.805	0.00	0.00
ATOM	60	O	CYS	7	11.653	4.083	-6.616	0.00	0.00
ATOM	61	N	ILE	8	10.477	5.155	-8.222	0.00	0.00
ATOM	62	H	ILE	8	10.302	5.265	-9.212	0.00	0.00
ATOM	63	CA	ILE	8	9.741	6.010	-7.292	0.00	0.00
ATOM	64	CB	ILE	8	9.018	7.206	-7.957	0.00	0.00
ATOM	65	CG2	ILE	8	10.056	8.149	-8.595	0.00	0.00
ATOM	66	CG1	ILE	8	7.912	6.794	-8.950	0.00	0.00
ATOM	67	CD1	ILE	8	7.033	7.955	-9.431	0.00	0.00
ATOM	68	C	ILE	8	8.822	5.213	-6.360	0.00	0.00
ATOM	69	O	ILE	8	8.715	5.561	-5.187	0.00	0.00
ATOM	70	N	SER	9	8.223	4.116	-6.842	0.00	0.00
ATOM	71	H	SER	9	8.348	3.884	-7.819	0.00	0.00
ATOM	72	CA	SER	9	7.430	3.207	-6.022	0.00	0.00
ATOM	73	CB	SER	9	6.746	2.198	-6.952	0.00	0.00
ATOM	74	OG	SER	9	5.880	1.355	-6.222	0.00	0.00
ATOM	75	HG	SER	9	5.455	0.749	-6.834	0.00	0.00
ATOM	76	C	SER	9	8.299	2.487	-4.981	0.00	0.00
ATOM	77	O	SER	9	7.865	2.322	-3.841	0.00	0.00
ATOM	78	N	VAL	10	9.527	2.092	-5.355	0.00	0.00
ATOM	79	H	VAL	10	9.822	2.259	-6.308	0.00	0.00
ATOM	80	CA	VAL	10	10.488	1.439	-4.467	0.00	0.00
ATOM	81	CB	VAL	10	11.590	0.739	-5.301	0.00	0.00
ATOM	82	CG1	VAL	10	12.857	0.370	-4.510	0.00	0.00
ATOM	83	CG2	VAL	10	11.028	-0.564	-5.898	0.00	0.00
ATOM	84	C	VAL	10	11.045	2.397	-3.397	0.00	0.00
ATOM	85	O	VAL	10	11.425	1.934	-2.323	0.00	0.00
ATOM	86	N	LEU	11	11.046	3.718	-3.626	0.00	0.00
ATOM	87	H	LEU	11	10.741	4.069	-4.523	0.00	0.00
ATOM	88	CA	LEU	11	11.403	4.680	-2.585	0.00	0.00
ATOM	89	CB	LEU	11	11.629	6.081	-3.186	0.00	0.00
ATOM	90	CG	LEU	11	12.881	6.204	-4.080	0.00	0.00
ATOM	91	CD1	LEU	11	12.881	7.571	-4.779	0.00	0.00
ATOM	92	CD2	LEU	11	14.187	6.047	-3.287	0.00	0.00
ATOM	93	C	LEU	11	10.331	4.735	-1.493	0.00	0.00
ATOM	94	O	LEU	11	10.673	4.708	-0.310	0.00	0.00
ATOM	95	N	LEU	12	9.046	4.773	-1.879	0.00	0.00
ATOM	96	H	LEU	12	8.829	4.798	-2.866	0.00	0.00
ATOM	97	CA	LEU	12	7.933	4.712	-0.936	0.00	0.00
ATOM	98	CB	LEU	12	6.609	5.114	-1.618	0.00	0.00
ATOM	99	CG	LEU	12	6.349	6.629	-1.800	0.00	0.00
ATOM	100	CD1	LEU	12	6.475	7.424	-0.490	0.00	0.00
ATOM	101	CD2	LEU	12	7.205	7.290	-2.885	0.00	0.00
ATOM	102	C	LEU	12	7.813	3.333	-0.273	0.00	0.00
ATOM	103	O	LEU	12	7.270	3.253	0.827	0.00	0.00
ATOM	104	N	SER	13	8.359	2.271	-0.884	0.00	0.00
ATOM	105	H	SER	13	8.775	2.394	-1.797	0.00	0.00
ATOM	106	CA	SER	13	8.421	0.946	-0.280	0.00	0.00
ATOM	107	CB	SER	13	8.951	-0.077	-1.282	0.00	0.00
ATOM	108	OG	SER	13	9.099	-1.310	-0.623	0.00	0.00
ATOM	109	HG	SER	13	9.427	-1.956	-1.252	0.00	0.00
ATOM	110	C	SER	13	9.273	0.950	0.990	0.00	0.00
ATOM	111	O	SER	13	8.819	0.466	2.026	0.00	0.00
ATOM	112	N	LEU	14	10.492	1.503	0.918	0.00	0.00
ATOM	113	H	LEU	14	10.813	1.877	0.035	0.00	0.00
ATOM	114	CA	LEU	14	11.374	1.623	2.074	0.00	0.00
ATOM	115	CB	LEU	14	12.797	2.007	1.620	0.00	0.00
ATOM	116	CG	LEU	14	13.726	0.831	1.239	0.00	0.00
ATOM	117	CD1	LEU	14	14.038	-0.075	2.441	0.00	0.00
ATOM	118	CD2	LEU	14	13.201	-0.019	0.073	0.00	0.00
ATOM	119	C	LEU	14	10.837	2.631	3.101	0.00	0.00
ATOM	120	O	LEU	14	11.157	2.497	4.282	0.00	0.00
ATOM	121	N	THR	15	9.988	3.588	2.690	0.00	0.00
ATOM	122	H	THR	15	9.772	3.661	1.705	0.00	0.00

ATOM	123	CA	THR	15	9.285	4.477	3.614	0.00	0.00
ATOM	124	CB	THR	15	8.678	5.685	2.862	0.00	0.00
ATOM	125	CG2	THR	15	7.178	5.937	3.069	0.00	0.00
ATOM	126	OG1	THR	15	9.358	6.857	3.261	0.00	0.00
ATOM	127	HG1	THR	15	9.005	7.597	2.762	0.00	0.00
ATOM	128	C	THR	15	8.292	3.705	4.503	0.00	0.00
ATOM	129	O	THR	15	8.154	4.016	5.685	0.00	0.00
ATOM	130	N	VAL	16	7.654	2.667	3.948	0.00	0.00
ATOM	131	H	VAL	16	7.830	2.479	2.969	0.00	0.00
ATOM	132	CA	VAL	16	6.734	1.752	4.625	0.00	0.00
ATOM	133	CB	VAL	16	5.717	1.249	3.563	0.00	0.00
ATOM	134	CG1	VAL	16	4.800	0.106	4.030	0.00	0.00
ATOM	135	CG2	VAL	16	4.835	2.427	3.122	0.00	0.00
ATOM	136	C	VAL	16	7.478	0.592	5.321	0.00	0.00
ATOM	137	O	VAL	16	6.869	-0.166	6.077	0.00	0.00
ATOM	138	N	PHE	17	8.795	0.456	5.118	0.00	0.00
ATOM	139	H	PHE	17	9.260	1.083	4.476	0.00	0.00
ATOM	140	CA	PHE	17	9.611	-0.530	5.817	0.00	0.00
ATOM	141	CB	PHE	17	10.708	-1.033	4.870	0.00	0.00
ATOM	142	CG	PHE	17	11.522	-2.193	5.415	0.00	0.00
ATOM	143	CD1	PHE	17	12.914	-2.068	5.585	0.00	0.00
ATOM	144	CE1	PHE	17	13.666	-3.150	6.076	0.00	0.00
ATOM	145	CZ	PHE	17	13.028	-4.358	6.409	0.00	0.00
ATOM	146	CE2	PHE	17	11.637	-4.484	6.249	0.00	0.00
ATOM	147	CD2	PHE	17	10.886	-3.405	5.750	0.00	0.00
ATOM	148	C	PHE	17	10.230	0.041	7.098	0.00	0.00
ATOM	149	O	PHE	17	10.403	-0.691	8.068	0.00	0.00
ATOM	150	N	LEU	18	10.526	1.346	7.130	0.00	0.00
ATOM	151	H	LEU	18	10.403	1.897	6.291	0.00	0.00
ATOM	152	CA	LEU	18	10.896	2.050	8.354	0.00	0.00
ATOM	153	CB	LEU	18	11.530	3.403	7.987	0.00	0.00
ATOM	154	CG	LEU	18	12.879	3.286	7.245	0.00	0.00
ATOM	155	CD1	LEU	18	13.301	4.670	6.731	0.00	0.00
ATOM	156	CD2	LEU	18	13.990	2.715	8.140	0.00	0.00
ATOM	157	C	LEU	18	9.673	2.268	9.259	0.00	0.00
ATOM	158	O	LEU	18	9.849	2.384	10.469	0.00	0.00
ATOM	159	N	LEU	19	8.455	2.272	8.688	0.00	0.00
ATOM	160	H	LEU	19	8.412	2.195	7.682	0.00	0.00
ATOM	161	CA	LEU	19	7.175	2.286	9.391	0.00	0.00
ATOM	162	CB	LEU	19	6.037	2.266	8.350	0.00	0.00
ATOM	163	CG	LEU	19	4.564	2.181	8.822	0.00	0.00
ATOM	164	CD1	LEU	19	3.673	2.526	7.617	0.00	0.00
ATOM	165	CD2	LEU	19	4.122	0.794	9.310	0.00	0.00
ATOM	166	C	LEU	19	7.100	1.105	10.352	0.00	0.00
ATOM	167	O	LEU	19	7.062	1.310	11.560	0.00	0.00
ATOM	168	N	VAL	20	7.099	-0.124	9.817	0.00	0.00
ATOM	169	H	VAL	20	7.136	-0.212	8.812	0.00	0.00
ATOM	170	CA	VAL	20	7.026	-1.355	10.600	0.00	0.00
ATOM	171	CB	VAL	20	6.989	-2.580	9.653	0.00	0.00
ATOM	172	CG1	VAL	20	8.119	-2.645	8.621	0.00	0.00
ATOM	173	CG2	VAL	20	6.980	-3.921	10.402	0.00	0.00
ATOM	174	C	VAL	20	8.206	-1.469	11.574	0.00	0.00
ATOM	175	O	VAL	20	8.066	-2.124	12.595	0.00	0.00
ATOM	176	N	ILE	21	9.352	-0.836	11.298	0.00	0.00
ATOM	177	H	ILE	21	9.423	-0.304	10.442	0.00	0.00
ATOM	178	CA	ILE	21	10.528	-0.887	12.162	0.00	0.00
ATOM	179	CB	ILE	21	11.791	-0.637	11.286	0.00	0.00
ATOM	180	CG2	ILE	21	13.035	-0.126	12.041	0.00	0.00
ATOM	181	CG1	ILE	21	12.131	-1.951	10.542	0.00	0.00
ATOM	182	CD1	ILE	21	13.210	-1.823	9.459	0.00	0.00
ATOM	183	C	ILE	21	10.424	0.026	13.399	0.00	0.00
ATOM	184	O	ILE	21	11.224	-0.096	14.325	0.00	0.00
ATOM	185	N	THR	22	9.416	0.897	13.457	0.00	0.00
ATOM	186	H	THR	22	8.797	0.973	12.660	0.00	0.00
ATOM	187	CA	THR	22	9.194	1.847	14.547	0.00	0.00

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ATOM    188  CB  THR    22       9.414   3.264  14.009  0.00  0.00
ATOM    189  CG2 THR    22      10.872   3.533  13.616  0.00  0.00
ATOM    190  OG1 THR    22       8.581   3.498  12.893  0.00  0.00
ATOM    191  HG1 THR    22       8.828   4.336  12.498  0.00  0.00
ATOM    192  C   THR    22       7.815   1.661  15.193  0.00  0.00
ATOM    193  O   THR    22       7.609   2.107  16.321  0.00  0.00
ATOM    194  N   GLU    23       6.921   0.913  14.532  0.00  0.00
ATOM    195  H   GLU    23       7.134   0.672  13.574  0.00  0.00
ATOM    196  CA  GLU    23       5.869   0.133  15.163  0.00  0.00
ATOM    197  CB  GLU    23       4.942  -0.441  14.072  0.00  0.00
ATOM    198  CG  GLU    23       4.169   0.583  13.237  0.00  0.00
ATOM    199  CD  GLU    23       3.536   1.675  14.085  0.00  0.00
ATOM    200  OE1 GLU    23       3.811   2.853  13.765  0.00  0.00
ATOM    201  OE2 GLU    23       2.807   1.311  15.035  0.00  0.00
ATOM    202  C   GLU    23       6.524  -1.009  15.951  0.00  0.00
ATOM    203  O   GLU    23       6.407  -1.064  17.174  0.00  0.00
ATOM    204  N   THR    24       7.207  -1.911  15.230  0.00  0.00
ATOM    205  H   THR    24       7.247  -1.772  14.230  0.00  0.00
ATOM    206  CA  THR    24       7.853  -3.115  15.730  0.00  0.00
ATOM    207  CB  THR    24       7.648  -4.324  14.798  0.00  0.00
ATOM    208  CG2 THR    24       8.232  -5.603  15.416  0.00  0.00
ATOM    209  OG1 THR    24       6.269  -4.511  14.554  0.00  0.00
ATOM    210  HG1 THR    24       6.167  -5.285  13.990  0.00  0.00
ATOM    211  C   THR    24       9.332  -2.850  16.043  0.00  0.00
ATOM    212  O   THR    24       9.669  -2.599  17.199  0.00  0.00
ATOM    213  N   NME    25      10.210  -2.958  15.034  0.00  0.00
ATOM    214  H   NME    25       9.852  -3.136  14.107  0.00  0.00
ATOM    215  CA  NME    25      11.655  -2.967  15.204  0.00  0.00
TER
ATOM    216  CA  ACE    26      -2.283  10.455 -18.657  0.00  0.00
ATOM    217  C   ACE    26      -1.621  10.026 -17.355  0.00  0.00
ATOM    218  O   ACE    26      -2.076  10.406 -16.276  0.00  0.00
ATOM    219  N   GLU    27      -0.535   9.247 -17.473  0.00  0.00
ATOM    220  H   GLU    27      -0.238   8.982 -18.401  0.00  0.00
ATOM    221  CA  GLU    27       0.219   8.675 -16.354  0.00  0.00
ATOM    222  CB  GLU    27       1.299   7.732 -16.918  0.00  0.00
ATOM    223  CG  GLU    27       2.095   6.942 -15.861  0.00  0.00
ATOM    224  CD  GLU    27       1.211   6.217 -14.838  0.00  0.00
ATOM    225  OE1 GLU    27       1.511   6.346 -13.630  0.00  0.00
ATOM    226  OE2 GLU    27       0.245   5.554 -15.275  0.00  0.00
ATOM    227  C   GLU    27       0.813   9.739 -15.411  0.00  0.00
ATOM    228  O   GLU    27       1.147   9.425 -14.273  0.00  0.00
ATOM    229  N   LYS    28       0.913  11.001 -15.851  0.00  0.00
ATOM    230  H   LYS    28       0.598  11.204 -16.789  0.00  0.00
ATOM    231  CA  LYS    28       1.469  12.100 -15.071  0.00  0.00
ATOM    232  CB  LYS    28       1.786  13.290 -15.996  0.00  0.00
ATOM    233  CG  LYS    28       3.109  13.161 -16.775  0.00  0.00
ATOM    234  CD  LYS    28       3.135  12.037 -17.826  0.00  0.00
ATOM    235  CE  LYS    28       4.426  12.051 -18.653  0.00  0.00
ATOM    236  NZ  LYS    28       4.509  13.225 -19.543  0.00  0.00
ATOM    237  HZ1 LYS    28       4.489  14.071 -18.991  0.00  0.00
ATOM    238  HZ2 LYS    28       5.370  13.192 -20.071  0.00  0.00
ATOM    239  HZ3 LYS    28       3.726  13.225 -20.181  0.00  0.00
ATOM    240  C   LYS    28       0.543  12.544 -13.934  0.00  0.00
ATOM    241  O   LYS    28       1.027  12.826 -12.838  0.00  0.00
ATOM    242  N   MET    29      -0.774  12.590 -14.176  0.00  0.00
ATOM    243  H   MET    29      -1.112  12.342 -15.095  0.00  0.00
ATOM    244  CA  MET    29      -1.764  12.813 -13.125  0.00  0.00
ATOM    245  CB  MET    29      -3.085  13.267 -13.769  0.00  0.00
ATOM    246  CG  MET    29      -4.161  13.651 -12.744  0.00  0.00
ATOM    247  SD  MET    29      -3.692  14.972 -11.590  0.00  0.00
ATOM    248  CE  MET    29      -5.246  15.139 -10.676  0.00  0.00
ATOM    249  C   MET    29      -1.955  11.542 -12.291  0.00  0.00
ATOM    250  O   MET    29      -2.253  11.652 -11.107  0.00  0.00
ATOM    251  N   THR    30      -1.747  10.351 -12.877  0.00  0.00
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ATOM	252	H	THR	30	-1.520	10.320	-13.862	0.00	0.00
ATOM	253	CA	THR	30	-1.852	9.072	-12.179	0.00	0.00
ATOM	254	CB	THR	30	-1.754	7.896	-13.169	0.00	0.00
ATOM	255	CG2	THR	30	-1.994	6.541	-12.493	0.00	0.00
ATOM	256	OG1	THR	30	-2.715	8.038	-14.195	0.00	0.00
ATOM	257	HG1	THR	30	-2.650	7.272	-14.770	0.00	0.00
ATOM	258	C	THR	30	-0.788	8.952	-11.081	0.00	0.00
ATOM	259	O	THR	30	-1.121	8.605	-9.948	0.00	0.00
ATOM	260	N	LEU	31	0.480	9.258	-11.400	0.00	0.00
ATOM	261	H	LEU	31	0.706	9.505	-12.355	0.00	0.00
ATOM	262	CA	LEU	31	1.562	9.251	-10.421	0.00	0.00
ATOM	263	CB	LEU	31	2.937	9.148	-11.113	0.00	0.00
ATOM	264	CG	LEU	31	3.392	10.353	-11.965	0.00	0.00
ATOM	265	CD1	LEU	31	4.096	11.445	-11.142	0.00	0.00
ATOM	266	CD2	LEU	31	4.365	9.882	-13.057	0.00	0.00
ATOM	267	C	LEU	31	1.454	10.399	-9.416	0.00	0.00
ATOM	268	O	LEU	31	1.930	10.247	-8.295	0.00	0.00
ATOM	269	N	CYS	32	0.786	11.507	-9.773	0.00	0.00
ATOM	270	H	CYS	32	0.420	11.576	-10.712	0.00	0.00
ATOM	271	CA	CYS	32	0.488	12.593	-8.848	0.00	0.00
ATOM	272	CB	CYS	32	-0.021	13.806	-9.638	0.00	0.00
ATOM	273	SG	CYS	32	-0.259	15.217	-8.524	0.00	0.00
ATOM	274	HG	CYS	32	-0.695	16.067	-9.459	0.00	0.00
ATOM	275	C	CYS	32	-0.529	12.134	-7.800	0.00	0.00
ATOM	276	O	CYS	32	-0.267	12.312	-6.612	0.00	0.00
ATOM	277	N	ILE	33	-1.659	11.529	-8.216	0.00	0.00
ATOM	278	H	ILE	33	-1.826	11.401	-9.205	0.00	0.00
ATOM	279	CA	ILE	33	-2.684	11.082	-7.275	0.00	0.00
ATOM	280	CB	ILE	33	-4.048	10.729	-7.917	0.00	0.00
ATOM	281	CG2	ILE	33	-4.660	11.993	-8.547	0.00	0.00
ATOM	282	CG1	ILE	33	-3.996	9.546	-8.906	0.00	0.00
ATOM	283	CD1	ILE	33	-5.371	9.049	-9.368	0.00	0.00
ATOM	284	C	ILE	33	-2.165	9.989	-6.339	0.00	0.00
ATOM	285	O	ILE	33	-2.443	10.052	-5.146	0.00	0.00
ATOM	286	N	SER	34	-1.357	9.045	-6.837	0.00	0.00
ATOM	287	H	SER	34	-1.155	9.048	-7.828	0.00	0.00
ATOM	288	CA	SER	34	-0.735	8.012	-6.015	0.00	0.00
ATOM	289	CB	SER	34	0.006	7.043	-6.945	0.00	0.00
ATOM	290	OG	SER	34	0.534	5.957	-6.216	0.00	0.00
ATOM	291	HG	SER	34	0.980	5.365	-6.827	0.00	0.00
ATOM	292	C	SER	34	0.223	8.612	-4.976	0.00	0.00
ATOM	293	O	SER	34	0.245	8.145	-3.839	0.00	0.00
ATOM	294	N	VAL	35	0.977	9.659	-5.348	0.00	0.00
ATOM	295	H	VAL	35	0.909	9.995	-6.300	0.00	0.00
ATOM	296	CA	VAL	35	1.896	10.368	-4.458	0.00	0.00
ATOM	297	CB	VAL	35	2.886	11.226	-5.285	0.00	0.00
ATOM	298	CG1	VAL	35	3.608	12.321	-4.481	0.00	0.00
ATOM	299	CG2	VAL	35	3.967	10.314	-5.894	0.00	0.00
ATOM	300	C	VAL	35	1.161	11.169	-3.369	0.00	0.00
ATOM	301	O	VAL	35	1.709	11.328	-2.279	0.00	0.00
ATOM	302	N	LEU	36	-0.080	11.622	-3.604	0.00	0.00
ATOM	303	H	LEU	36	-0.499	11.480	-4.513	0.00	0.00
ATOM	304	CA	LEU	36	-0.880	12.257	-2.558	0.00	0.00
ATOM	305	CB	LEU	36	-2.151	12.903	-3.141	0.00	0.00
ATOM	306	CG	LEU	36	-1.895	14.123	-4.052	0.00	0.00
ATOM	307	CD1	LEU	36	-3.205	14.536	-4.738	0.00	0.00
ATOM	308	CD2	LEU	36	-1.332	15.324	-3.278	0.00	0.00
ATOM	309	C	LEU	36	-1.235	11.257	-1.456	0.00	0.00
ATOM	310	O	LEU	36	-1.056	11.566	-0.279	0.00	0.00
ATOM	311	N	LEU	37	-1.689	10.055	-1.837	0.00	0.00
ATOM	312	H	LEU	37	-1.806	9.870	-2.825	0.00	0.00
ATOM	313	CA	LEU	37	-1.984	8.972	-0.906	0.00	0.00
ATOM	314	CB	LEU	37	-2.887	7.925	-1.582	0.00	0.00
ATOM	315	CG	LEU	37	-4.345	8.358	-1.869	0.00	0.00
ATOM	316	CD1	LEU	37	-5.010	9.090	-0.690	0.00	0.00

ATOM	317	CD2	LEU	37	-4.546	9.184	-3.141	0.00	0.00
ATOM	318	C	LEU	37	-0.716	8.338	-0.311	0.00	0.00
ATOM	319	O	LEU	37	-0.817	7.630	0.692	0.00	0.00
ATOM	320	N	ALA	38	0.471	8.626	-0.867	0.00	0.00
ATOM	321	H	ALA	38	0.497	9.193	-1.702	0.00	0.00
ATOM	322	CA	ALA	38	1.740	8.226	-0.280	0.00	0.00
ATOM	323	CB	ALA	38	2.864	8.324	-1.312	0.00	0.00
ATOM	324	C	ALA	38	2.066	9.043	0.973	0.00	0.00
ATOM	325	O	ALA	38	2.474	8.464	1.980	0.00	0.00
ATOM	326	N	LEU	39	1.855	10.367	0.926	0.00	0.00
ATOM	327	H	LEU	39	1.526	10.778	0.063	0.00	0.00
ATOM	328	CA	LEU	39	2.012	11.251	2.080	0.00	0.00
ATOM	329	CB	LEU	39	2.100	12.720	1.618	0.00	0.00
ATOM	330	CG	LEU	39	3.511	13.226	1.241	0.00	0.00
ATOM	331	CD1	LEU	39	4.467	13.237	2.446	0.00	0.00
ATOM	332	CD2	LEU	39	4.151	12.457	0.077	0.00	0.00
ATOM	333	C	LEU	39	0.881	11.068	3.102	0.00	0.00
ATOM	334	O	LEU	39	1.101	11.338	4.283	0.00	0.00
ATOM	335	N	THR	40	-0.291	10.561	2.686	0.00	0.00
ATOM	336	H	THR	40	-0.432	10.397	1.699	0.00	0.00
ATOM	337	CA	THR	40	-1.360	10.158	3.602	0.00	0.00
ATOM	338	CB	THR	40	-2.627	9.753	2.826	0.00	0.00
ATOM	339	CG2	THR	40	-3.778	9.334	3.747	0.00	0.00
ATOM	340	OG1	THR	40	-3.079	10.847	2.055	0.00	0.00
ATOM	341	HG1	THR	40	-3.887	10.588	1.606	0.00	0.00
ATOM	342	C	THR	40	-0.873	9.037	4.530	0.00	0.00
ATOM	343	O	THR	40	-1.089	9.092	5.741	0.00	0.00
ATOM	344	N	PHE	41	-0.182	8.048	3.954	0.00	0.00
ATOM	345	H	PHE	41	-0.043	8.088	2.953	0.00	0.00
ATOM	346	CA	PHE	41	0.382	6.891	4.637	0.00	0.00
ATOM	347	CB	PHE	41	0.495	5.780	3.579	0.00	0.00
ATOM	348	CG	PHE	41	0.506	4.374	4.138	0.00	0.00
ATOM	349	CD1	PHE	41	-0.701	3.756	4.512	0.00	0.00
ATOM	350	CE1	PHE	41	-0.689	2.457	5.050	0.00	0.00
ATOM	351	CZ	PHE	41	0.523	1.771	5.204	0.00	0.00
ATOM	352	CE2	PHE	41	1.723	2.376	4.804	0.00	0.00
ATOM	353	CD2	PHE	41	1.717	3.679	4.279	0.00	0.00
ATOM	354	C	PHE	41	1.737	7.181	5.315	0.00	0.00
ATOM	355	O	PHE	41	2.285	6.307	5.986	0.00	0.00
ATOM	356	N	PHE	42	2.270	8.402	5.164	0.00	0.00
ATOM	357	H	PHE	42	1.783	9.065	4.577	0.00	0.00
ATOM	358	CA	PHE	42	3.482	8.875	5.827	0.00	0.00
ATOM	359	CB	PHE	42	4.246	9.781	4.851	0.00	0.00
ATOM	360	CG	PHE	42	5.642	10.167	5.296	0.00	0.00
ATOM	361	CD1	PHE	42	5.921	11.481	5.719	0.00	0.00
ATOM	362	CE1	PHE	42	7.227	11.835	6.101	0.00	0.00
ATOM	363	CZ	PHE	42	8.255	10.876	6.071	0.00	0.00
ATOM	364	CE2	PHE	42	7.980	9.564	5.650	0.00	0.00
ATOM	365	CD2	PHE	42	6.676	9.213	5.258	0.00	0.00
ATOM	366	C	PHE	42	3.150	9.624	7.120	0.00	0.00
ATOM	367	O	PHE	42	3.879	9.495	8.097	0.00	0.00
ATOM	368	N	LEU	43	2.031	10.360	7.154	0.00	0.00
ATOM	369	H	LEU	43	1.484	10.457	6.309	0.00	0.00
ATOM	370	CA	LEU	43	1.473	10.924	8.382	0.00	0.00
ATOM	371	CB	LEU	43	0.398	11.963	8.019	0.00	0.00
ATOM	372	CG	LEU	43	0.943	13.203	7.276	0.00	0.00
ATOM	373	CD1	LEU	43	-0.231	14.055	6.775	0.00	0.00
ATOM	374	CD2	LEU	43	1.853	14.063	8.168	0.00	0.00
ATOM	375	C	LEU	43	0.874	9.828	9.281	0.00	0.00
ATOM	376	O	LEU	43	0.769	10.036	10.491	0.00	0.00
ATOM	377	N	LEU	44	0.536	8.658	8.710	0.00	0.00
ATOM	378	H	LEU	44	0.627	8.573	7.707	0.00	0.00
ATOM	379	CA	LEU	44	0.132	7.461	9.440	0.00	0.00
ATOM	380	CB	LEU	44	-0.237	6.330	8.461	0.00	0.00
ATOM	381	CG	LEU	44	-0.598	4.940	9.053	0.00	0.00

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ATOM    382  CD1 LEU    44      -1.120   4.095   7.887  0.00  0.00
ATOM    383  CD2 LEU    44       0.548   4.126   9.682  0.00  0.00
ATOM    384  C   LEU    44       1.236   7.030  10.392  0.00  0.00
ATOM    385  O   LEU    44       1.015   7.010  11.603  0.00  0.00
ATOM    386  N   LEU    45       2.406   6.671   9.845  0.00  0.00
ATOM    387  H   LEU    45       2.516   6.707   8.841  0.00  0.00
ATOM    388  CA  LEU    45       3.519   6.170  10.638  0.00  0.00
ATOM    389  CB  LEU    45       4.613   5.598   9.712  0.00  0.00
ATOM    390  CG  LEU    45       5.541   6.618   9.012  0.00  0.00
ATOM    391  CD1 LEU    45       6.887   6.784   9.737  0.00  0.00
ATOM    392  CD2 LEU    45       5.832   6.220   7.559  0.00  0.00
ATOM    393  C   LEU    45       4.079   7.261  11.561  0.00  0.00
ATOM    394  O   LEU    45       4.821   6.946  12.478  0.00  0.00
ATOM    395  N   ILE    46       3.724   8.534  11.345  0.00  0.00
ATOM    396  H   ILE    46       3.121   8.734  10.560  0.00  0.00
ATOM    397  CA  ILE    46       4.148   9.666  12.160  0.00  0.00
ATOM    398  CB  ILE    46       4.432  10.867  11.210  0.00  0.00
ATOM    399  CG2 ILE    46       4.416  12.260  11.869  0.00  0.00
ATOM    400  CG1 ILE    46       5.801  10.618  10.528  0.00  0.00
ATOM    401  CD1 ILE    46       6.159  11.602   9.409  0.00  0.00
ATOM    402  C   ILE    46       3.185   9.956  13.327  0.00  0.00
ATOM    403  O   ILE    46       3.473  10.794  14.180  0.00  0.00
ATOM    404  N   SER    47       2.082   9.209  13.426  0.00  0.00
ATOM    405  H   SER    47       1.886   8.542  12.690  0.00  0.00
ATOM    406  CA  SER    47       1.150   9.252  14.548  0.00  0.00
ATOM    407  CB  SER    47      -0.126   9.962  14.095  0.00  0.00
ATOM    408  OG  SER    47      -0.740   9.307  13.001  0.00  0.00
ATOM    409  HG  SER    47      -0.178   9.413  12.226  0.00  0.00
ATOM    410  C   SER    47       0.919   7.870  15.169  0.00  0.00
ATOM    411  O   SER    47       0.237   7.783  16.189  0.00  0.00
ATOM    412  N   LYS    48       1.561   6.825  14.617  0.00  0.00
ATOM    413  H   LYS    48       2.046   6.979  13.746  0.00  0.00
ATOM    414  CA  LYS    48       1.788   5.536  15.262  0.00  0.00
ATOM    415  CB  LYS    48       1.158   4.403  14.455  0.00  0.00
ATOM    416  CG  LYS    48      -0.354   4.284  14.642  0.00  0.00
ATOM    417  CD  LYS    48      -0.773   3.894  16.077  0.00  0.00
ATOM    418  CE  LYS    48      -1.189   5.103  16.921  0.00  0.00
ATOM    419  NZ  LYS    48      -1.702   4.693  18.239  0.00  0.00
ATOM    420  HZ1 LYS    48      -1.012   4.132  18.717  0.00  0.00
ATOM    421  HZ2 LYS    48      -1.914   5.513  18.789  0.00  0.00
ATOM    422  HZ3 LYS    48      -2.552   4.158  18.112  0.00  0.00
ATOM    423  C   LYS    48       3.272   5.283  15.588  0.00  0.00
ATOM    424  O   LYS    48       3.543   4.430  16.432  0.00  0.00
ATOM    425  N   ILE    49       4.204   6.096  15.057  0.00  0.00
ATOM    426  H   ILE    49       3.931   6.719  14.311  0.00  0.00
ATOM    427  CA  ILE    49       5.427   6.457  15.769  0.00  0.00
ATOM    428  CB  ILE    49       6.732   5.740  15.337  0.00  0.00
ATOM    429  CG2 ILE    49       7.308   6.108  13.955  0.00  0.00
ATOM    430  CG1 ILE    49       7.793   5.862  16.468  0.00  0.00
ATOM    431  CD1 ILE    49       8.665   7.127  16.501  0.00  0.00
ATOM    432  C   ILE    49       5.527   7.970  16.024  0.00  0.00
ATOM    433  O   ILE    49       5.311   8.399  17.157  0.00  0.00
ATOM    434  N   NME    50       5.876   8.773  15.013  0.00  0.00
ATOM    435  H   NME    50       5.998   8.361  14.099  0.00  0.00
ATOM    436  CA  NME    50       6.271  10.165  15.177  0.00  0.00
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ATOM    437  CA  ACE    51     -10.666   1.083 -18.631  0.00  0.00
ATOM    438  C   ACE    51     -10.046   1.575 -17.331  0.00  0.00
ATOM    439  O   ACE    51     -10.544   1.258 -16.251  0.00  0.00
ATOM    440  N   GLU    52      -8.968   2.364 -17.452  0.00  0.00
ATOM    441  H   GLU    52      -8.628   2.567 -18.381  0.00  0.00
ATOM    442  CA  GLU    52      -8.186   2.902 -16.335  0.00  0.00
ATOM    443  CB  GLU    52      -6.955   3.634 -16.901  0.00  0.00
ATOM    444  CG  GLU    52      -5.951   4.138 -15.847  0.00  0.00
ATOM    445  CD  GLU    52      -5.535   3.066 -14.831  0.00  0.00
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ATOM    446  OE1 GLU    52      -5.559    3.384  -13.621  0.00  0.00
ATOM    447  OE2 GLU    52      -5.211    1.942  -15.275  0.00  0.00
ATOM    448  C   GLU    52      -9.010    3.796  -15.388  0.00  0.00
ATOM    449  O   GLU    52      -8.603    4.015  -14.251  0.00  0.00
ATOM    450  N   LYS    53     -10.180    4.283  -15.824  0.00  0.00
ATOM    451  H   LYS    53     -10.473    4.046  -16.760  0.00  0.00
ATOM    452  CA  LYS    53     -11.053    5.150  -15.040  0.00  0.00
ATOM    453  CB  LYS    53     -12.089    5.818  -15.963  0.00  0.00
ATOM    454  CG  LYS    53     -11.559    7.029  -16.754  0.00  0.00
ATOM    455  CD  LYS    53     -10.494    6.696  -17.814  0.00  0.00
ATOM    456  CE  LYS    53     -10.117    7.919  -18.658  0.00  0.00
ATOM    457  NZ  LYS    53     -11.217    8.353  -19.541  0.00  0.00
ATOM    458  HZ1 LYS    53     -12.022    8.601  -18.983  0.00  0.00
ATOM    459  HZ2 LYS    53     -10.924    9.156  -20.080  0.00  0.00
ATOM    460  HZ3 LYS    53     -11.465    7.602  -20.169  0.00  0.00
ATOM    461  C   LYS    53     -11.761    4.405  -13.903  0.00  0.00
ATOM    462  O   LYS    53     -11.891    4.952  -12.809  0.00  0.00
ATOM    463  N   VAL    54     -12.200    3.164  -14.148  0.00  0.00
ATOM    464  H   VAL    54     -12.057    2.773  -15.068  0.00  0.00
ATOM    465  CA  VAL    54     -12.728    2.277  -13.112  0.00  0.00
ATOM    466  CB  VAL    54     -13.527    1.124  -13.765  0.00  0.00
ATOM    467  CG1 VAL    54     -14.079    0.140  -12.718  0.00  0.00
ATOM    468  CG2 VAL    54     -14.713    1.664  -14.584  0.00  0.00
ATOM    469  C   VAL    54     -11.569    1.741  -12.265  0.00  0.00
ATOM    470  O   VAL    54     -11.753    1.551  -11.068  0.00  0.00
ATOM    471  N   THR    55     -10.381    1.536  -12.859  0.00  0.00
ATOM    472  H   THR    55     -10.295    1.697  -13.853  0.00  0.00
ATOM    473  CA  THR    55      -9.194    1.046  -12.162  0.00  0.00
ATOM    474  CB  THR    55      -8.048    0.775  -13.155  0.00  0.00
ATOM    475  CG2 THR    55      -6.833    0.127  -12.482  0.00  0.00
ATOM    476  OG1 THR    55      -8.483   -0.094  -14.180  0.00  0.00
ATOM    477  HG1 THR    55      -7.736   -0.269  -14.758  0.00  0.00
ATOM    478  C   THR    55      -8.748    2.021  -11.065  0.00  0.00
ATOM    479  O   THR    55      -8.516    1.595   -9.933  0.00  0.00
ATOM    480  N   LEU    56      -8.652    3.321  -11.382  0.00  0.00
ATOM    481  H   LEU    56      -8.821    3.613  -12.336  0.00  0.00
ATOM    482  CA  LEU    56      -8.307    4.347  -10.403  0.00  0.00
ATOM    483  CB  LEU    56      -7.786    5.623  -11.095  0.00  0.00
ATOM    484  CG  LEU    56      -8.796    6.430  -11.941  0.00  0.00
ATOM    485  CD1 LEU    56      -9.612    7.436  -11.112  0.00  0.00
ATOM    486  CD2 LEU    56      -8.052    7.211  -13.035  0.00  0.00
ATOM    487  C   LEU    56      -9.428    4.598   -9.393  0.00  0.00
ATOM    488  O   LEU    56      -9.129    5.005   -8.274  0.00  0.00
ATOM    489  N   CYS    57     -10.690    4.306   -9.743  0.00  0.00
ATOM    490  H   CYS    57     -10.875    3.975  -10.679  0.00  0.00
ATOM    491  CA  CYS    57     -11.808    4.362   -8.810  0.00  0.00
ATOM    492  CB  CYS    57     -13.128    4.274   -9.585  0.00  0.00
ATOM    493  SG  CYS    57     -14.524    4.525   -8.455  0.00  0.00
ATOM    494  HG  CYS    57     -15.482    4.408   -9.379  0.00  0.00
ATOM    495  C   CYS    57     -11.684    3.250   -7.764  0.00  0.00
ATOM    496  O   CYS    57     -11.771    3.550   -6.575  0.00  0.00
ATOM    497  N   ILE    58     -11.457    1.991   -8.183  0.00  0.00
ATOM    498  H   ILE    58     -11.384    1.798   -9.172  0.00  0.00
ATOM    499  CA  ILE    58     -11.358    0.867   -7.251  0.00  0.00
ATOM    500  CB  ILE    58     -11.468   -0.528   -7.914  0.00  0.00
ATOM    501  CG2 ILE    58     -12.863   -0.690   -8.546  0.00  0.00
ATOM    502  CG1 ILE    58     -10.334   -0.841   -8.910  0.00  0.00
ATOM    503  CD1 ILE    58     -10.300   -2.298   -9.389  0.00  0.00
ATOM    504  C   ILE    58     -10.147    0.986   -6.321  0.00  0.00
ATOM    505  O   ILE    58     -10.272    0.671   -5.140  0.00  0.00
ATOM    506  N   SER    59      -9.013    1.503   -6.811  0.00  0.00
ATOM    507  H   SER    59      -8.973    1.742   -7.793  0.00  0.00
ATOM    508  CA  SER    59      -7.835    1.772   -5.994  0.00  0.00
ATOM    509  CB  SER    59      -6.690    2.182   -6.928  0.00  0.00
ATOM    510  OG  SER    59      -5.491    2.352   -6.204  0.00  0.00
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ATOM	511	HG	SER	59	-4.792	2.591	-6.818	0.00	0.00
ATOM	512	C	SER	59	-8.108	2.867	-4.953	0.00	0.00
ATOM	513	O	SER	59	-7.648	2.750	-3.818	0.00	0.00
ATOM	514	N	VAL	60	-8.876	3.905	-5.322	0.00	0.00
ATOM	515	H	VAL	60	-9.223	3.940	-6.272	0.00	0.00
ATOM	516	CA	VAL	60	-9.265	4.998	-4.432	0.00	0.00
ATOM	517	CB	VAL	60	-9.741	6.215	-5.265	0.00	0.00
ATOM	518	CG1	VAL	60	-10.541	7.263	-4.472	0.00	0.00
ATOM	519	CG2	VAL	60	-8.517	6.933	-5.864	0.00	0.00
ATOM	520	C	VAL	60	-10.280	4.554	-3.361	0.00	0.00
ATOM	521	O	VAL	60	-10.318	5.159	-2.290	0.00	0.00
ATOM	522	N	LEU	61	-11.052	3.480	-3.581	0.00	0.00
ATOM	523	H	LEU	61	-11.008	3.009	-4.474	0.00	0.00
ATOM	524	CA	LEU	61	-11.901	2.915	-2.534	0.00	0.00
ATOM	525	CB	LEU	61	-12.909	1.910	-3.123	0.00	0.00
ATOM	526	CG	LEU	61	-13.994	2.537	-4.025	0.00	0.00
ATOM	527	CD1	LEU	61	-14.799	1.424	-4.710	0.00	0.00
ATOM	528	CD2	LEU	61	-14.957	3.442	-3.241	0.00	0.00
ATOM	529	C	LEU	61	-11.060	2.250	-1.440	0.00	0.00
ATOM	530	O	LEU	61	-11.309	2.485	-0.258	0.00	0.00
ATOM	531	N	LEU	62	-10.049	1.457	-1.829	0.00	0.00
ATOM	532	H	LEU	62	-9.900	1.302	-2.817	0.00	0.00
ATOM	533	CA	LEU	62	-9.102	0.850	-0.897	0.00	0.00
ATOM	534	CB	LEU	62	-8.300	-0.270	-1.593	0.00	0.00
ATOM	535	CG	LEU	62	-9.018	-1.623	-1.814	0.00	0.00
ATOM	536	CD1	LEU	62	-9.643	-2.189	-0.530	0.00	0.00
ATOM	537	CD2	LEU	62	-10.062	-1.618	-2.934	0.00	0.00
ATOM	538	C	LEU	62	-8.155	1.886	-0.271	0.00	0.00
ATOM	539	O	LEU	62	-7.590	1.612	0.785	0.00	0.00
ATOM	540	N	SER	63	-8.017	3.082	-0.864	0.00	0.00
ATOM	541	H	SER	63	-8.482	3.248	-1.746	0.00	0.00
ATOM	542	CA	SER	63	-7.286	4.186	-0.257	0.00	0.00
ATOM	543	CB	SER	63	-7.134	5.342	-1.243	0.00	0.00
ATOM	544	OG	SER	63	-6.568	6.434	-0.563	0.00	0.00
ATOM	545	HG	SER	63	-6.465	7.161	-1.181	0.00	0.00
ATOM	546	C	SER	63	-7.974	4.660	1.024	0.00	0.00
ATOM	547	O	SER	63	-7.322	4.753	2.063	0.00	0.00
ATOM	548	N	LEU	64	-9.281	4.947	0.953	0.00	0.00
ATOM	549	H	LEU	64	-9.759	4.859	0.066	0.00	0.00
ATOM	550	CA	LEU	64	-10.062	5.363	2.111	0.00	0.00
ATOM	551	CB	LEU	64	-11.442	5.887	1.664	0.00	0.00
ATOM	552	CG	LEU	64	-11.507	7.384	1.285	0.00	0.00
ATOM	553	CD1	LEU	64	-11.224	8.300	2.487	0.00	0.00
ATOM	554	CD2	LEU	64	-10.589	7.768	0.116	0.00	0.00
ATOM	555	C	LEU	64	-10.212	4.225	3.132	0.00	0.00
ATOM	556	O	LEU	64	-10.375	4.517	4.317	0.00	0.00
ATOM	557	N	THR	65	-10.100	2.951	2.714	0.00	0.00
ATOM	558	H	THR	65	-9.981	2.765	1.727	0.00	0.00
ATOM	559	CA	THR	65	-10.084	1.818	3.641	0.00	0.00
ATOM	560	CB	THR	65	-10.415	0.492	2.913	0.00	0.00
ATOM	561	CG2	THR	65	-9.313	-0.575	2.884	0.00	0.00
ATOM	562	OG1	THR	65	-11.537	-0.097	3.538	0.00	0.00
ATOM	563	HG1	THR	65	-11.768	-0.893	3.055	0.00	0.00
ATOM	564	C	THR	65	-8.814	1.779	4.506	0.00	0.00
ATOM	565	O	THR	65	-8.851	1.294	5.636	0.00	0.00
ATOM	566	N	VAL	66	-7.719	2.353	3.997	0.00	0.00
ATOM	567	H	VAL	66	-7.786	2.732	3.062	0.00	0.00
ATOM	568	CA	VAL	66	-6.420	2.502	4.649	0.00	0.00
ATOM	569	CB	VAL	66	-5.352	2.198	3.567	0.00	0.00
ATOM	570	CG1	VAL	66	-3.925	2.559	3.978	0.00	0.00
ATOM	571	CG2	VAL	66	-5.379	0.698	3.225	0.00	0.00
ATOM	572	C	VAL	66	-6.284	3.892	5.313	0.00	0.00
ATOM	573	O	VAL	66	-5.310	4.144	6.024	0.00	0.00
ATOM	574	N	PHE	67	-7.276	4.781	5.148	0.00	0.00
ATOM	575	H	PHE	67	-8.047	4.538	4.543	0.00	0.00

ATOM	576	CA	PHE	67	-7.349	6.061	5.845	0.00	0.00
ATOM	577	CB	PHE	67	-7.920	7.118	4.892	0.00	0.00
ATOM	578	CG	PHE	67	-7.904	8.533	5.444	0.00	0.00
ATOM	579	CD1	PHE	67	-9.105	9.254	5.590	0.00	0.00
ATOM	580	CE1	PHE	67	-9.084	10.569	6.089	0.00	0.00
ATOM	581	CZ	PHE	67	-7.863	11.165	6.452	0.00	0.00
ATOM	582	CE2	PHE	67	-6.663	10.445	6.318	0.00	0.00
ATOM	583	CD2	PHE	67	-6.684	9.133	5.813	0.00	0.00
ATOM	584	C	PHE	67	-8.198	5.980	7.119	0.00	0.00
ATOM	585	O	PHE	67	-7.928	6.700	8.075	0.00	0.00
ATOM	586	N	LEU	68	-9.194	5.085	7.164	0.00	0.00
ATOM	587	H	LEU	68	-9.408	4.549	6.335	0.00	0.00
ATOM	588	CA	LEU	68	-9.898	4.738	8.397	0.00	0.00
ATOM	589	CB	LEU	68	-11.193	3.986	8.045	0.00	0.00
ATOM	590	CG	LEU	68	-12.237	4.842	7.296	0.00	0.00
ATOM	591	CD1	LEU	68	-13.375	3.941	6.799	0.00	0.00
ATOM	592	CD2	LEU	68	-12.818	5.958	8.179	0.00	0.00
ATOM	593	C	LEU	68	-9.014	3.871	9.307	0.00	0.00
ATOM	594	O	LEU	68	-9.191	3.913	10.521	0.00	0.00
ATOM	595	N	LEU	69	-8.046	3.136	8.730	0.00	0.00
ATOM	596	H	LEU	69	-7.987	3.155	7.722	0.00	0.00
ATOM	597	CA	LEU	69	-7.027	2.348	9.420	0.00	0.00
ATOM	598	CB	LEU	69	-6.105	1.703	8.363	0.00	0.00
ATOM	599	CG	LEU	69	-4.888	0.869	8.834	0.00	0.00
ATOM	600	CD1	LEU	69	-4.375	0.064	7.628	0.00	0.00
ATOM	601	CD2	LEU	69	-3.704	1.695	9.357	0.00	0.00
ATOM	602	C	LEU	69	-6.243	3.221	10.394	0.00	0.00
ATOM	603	O	LEU	69	-6.277	2.978	11.599	0.00	0.00
ATOM	604	N	VAL	70	-5.545	4.233	9.858	0.00	0.00
ATOM	605	H	VAL	70	-5.571	4.347	8.854	0.00	0.00
ATOM	606	CA	VAL	70	-4.762	5.203	10.615	0.00	0.00
ATOM	607	CB	VAL	70	-4.039	6.171	9.644	0.00	0.00
ATOM	608	CG1	VAL	70	-4.936	6.845	8.604	0.00	0.00
ATOM	609	CG2	VAL	70	-3.279	7.289	10.371	0.00	0.00
ATOM	610	C	VAL	70	-5.649	5.978	11.595	0.00	0.00
ATOM	611	O	VAL	70	-5.145	6.438	12.606	0.00	0.00
ATOM	612	N	ILE	71	-6.953	6.123	11.333	0.00	0.00
ATOM	613	H	ILE	71	-7.330	5.720	10.486	0.00	0.00
ATOM	614	CA	ILE	71	-7.867	6.881	12.184	0.00	0.00
ATOM	615	CB	ILE	71	-8.994	7.473	11.285	0.00	0.00
ATOM	616	CG2	ILE	71	-10.325	7.793	11.995	0.00	0.00
ATOM	617	CG1	ILE	71	-8.441	8.747	10.601	0.00	0.00
ATOM	618	CD1	ILE	71	-9.348	9.356	9.524	0.00	0.00
ATOM	619	C	ILE	71	-8.368	6.088	13.406	0.00	0.00
ATOM	620	O	ILE	71	-8.968	6.678	14.304	0.00	0.00
ATOM	621	N	THR	72	-8.079	4.786	13.497	0.00	0.00
ATOM	622	H	THR	72	-7.620	4.331	12.719	0.00	0.00
ATOM	623	CA	THR	72	-8.423	3.957	14.657	0.00	0.00
ATOM	624	CB	THR	72	-9.641	3.075	14.346	0.00	0.00
ATOM	625	CG2	THR	72	-10.949	3.875	14.377	0.00	0.00
ATOM	626	OG1	THR	72	-9.535	2.482	13.069	0.00	0.00
ATOM	627	HG1	THR	72	-10.353	2.020	12.878	0.00	0.00
ATOM	628	C	THR	72	-7.221	3.219	15.258	0.00	0.00
ATOM	629	O	THR	72	-7.312	2.686	16.361	0.00	0.00
ATOM	630	N	GLU	73	-6.070	3.306	14.587	0.00	0.00
ATOM	631	H	GLU	73	-6.119	3.677	13.648	0.00	0.00
ATOM	632	CA	GLU	73	-4.733	3.301	15.164	0.00	0.00
ATOM	633	CB	GLU	73	-3.762	3.156	13.982	0.00	0.00
ATOM	634	CG	GLU	73	-3.490	1.699	13.589	0.00	0.00
ATOM	635	CD	GLU	73	-2.451	1.055	14.506	0.00	0.00
ATOM	636	OE1	GLU	73	-2.795	0.776	15.677	0.00	0.00
ATOM	637	OE2	GLU	73	-1.312	0.867	14.029	0.00	0.00
ATOM	638	C	GLU	73	-4.533	4.614	15.932	0.00	0.00
ATOM	639	O	GLU	73	-4.423	4.592	17.156	0.00	0.00
ATOM	640	N	THR	74	-4.509	5.746	15.211	0.00	0.00

ATOM	641	H	THR	74	-4.599	5.666	14.208	0.00	0.00
ATOM	642	CA	THR	74	-4.364	7.101	15.736	0.00	0.00
ATOM	643	CB	THR	74	-3.619	8.038	14.767	0.00	0.00
ATOM	644	CG2	THR	74	-3.335	9.399	15.417	0.00	0.00
ATOM	645	OG1	THR	74	-2.398	7.442	14.386	0.00	0.00
ATOM	646	HG1	THR	74	-1.910	8.067	13.839	0.00	0.00
ATOM	647	C	THR	74	-5.716	7.672	16.183	0.00	0.00
ATOM	648	O	THR	74	-6.035	7.610	17.370	0.00	0.00
ATOM	649	N	NME	75	-6.476	8.270	15.254	0.00	0.00
ATOM	650	H	NME	75	-6.161	8.257	14.295	0.00	0.00
ATOM	651	CA	NME	75	-7.656	9.066	15.556	0.00	0.00
ATOM	652	CA	ACE	76	-4.045	-8.929	-19.241	0.00	0.00
ATOM	653	C	ACE	76	-4.015	-8.111	-17.958	0.00	0.00
ATOM	654	O	ACE	76	-2.949	-7.910	-17.379	0.00	0.00
ATOM	655	N	GLU	77	-5.198	-7.652	-17.527	0.00	0.00
ATOM	656	H	GLU	77	-6.010	-7.846	-18.092	0.00	0.00
ATOM	657	CA	GLU	77	-5.391	-6.805	-16.347	0.00	0.00
ATOM	658	CB	GLU	77	-5.703	-5.373	-16.827	0.00	0.00
ATOM	659	CG	GLU	77	-5.866	-4.312	-15.722	0.00	0.00
ATOM	660	CD	GLU	77	-4.715	-4.292	-14.708	0.00	0.00
ATOM	661	OE1	GLU	77	-5.022	-4.256	-13.496	0.00	0.00
ATOM	662	OE2	GLU	77	-3.548	-4.318	-15.156	0.00	0.00
ATOM	663	C	GLU	77	-6.465	-7.361	-15.396	0.00	0.00
ATOM	664	O	GLU	77	-6.549	-6.921	-14.253	0.00	0.00
ATOM	665	N	LYS	78	-7.269	-8.342	-15.829	0.00	0.00
ATOM	666	H	LYS	78	-7.144	-8.695	-16.766	0.00	0.00
ATOM	667	CA	LYS	78	-8.386	-8.870	-15.048	0.00	0.00
ATOM	668	CB	LYS	78	-9.379	-9.594	-15.976	0.00	0.00
ATOM	669	CG	LYS	78	-10.375	-8.657	-16.686	0.00	0.00
ATOM	670	CD	LYS	78	-9.740	-7.666	-17.677	0.00	0.00
ATOM	671	CE	LYS	78	-10.794	-6.833	-18.416	0.00	0.00
ATOM	672	NZ	LYS	78	-11.598	-7.646	-19.349	0.00	0.00
ATOM	673	HZ1	LYS	78	-12.083	-8.370	-18.837	0.00	0.00
ATOM	674	HZ2	LYS	78	-12.275	-7.058	-19.816	0.00	0.00
ATOM	675	HZ3	LYS	78	-10.994	-8.071	-20.038	0.00	0.00
ATOM	676	C	LYS	78	-7.926	-9.797	-13.917	0.00	0.00
ATOM	677	O	LYS	78	-8.500	-9.752	-12.830	0.00	0.00
ATOM	678	N	MET	79	-6.883	-10.604	-14.152	0.00	0.00
ATOM	679	H	MET	79	-6.466	-10.607	-15.071	0.00	0.00
ATOM	680	CA	MET	79	-6.210	-11.357	-13.097	0.00	0.00
ATOM	681	CB	MET	79	-5.404	-12.502	-13.733	0.00	0.00
ATOM	682	CG	MET	79	-4.757	-13.440	-12.706	0.00	0.00
ATOM	683	SD	MET	79	-5.911	-14.233	-11.550	0.00	0.00
ATOM	684	CE	MET	79	-4.751	-15.290	-10.646	0.00	0.00
ATOM	685	C	MET	79	-5.312	-10.435	-12.263	0.00	0.00
ATOM	686	O	MET	79	-5.123	-10.703	-11.082	0.00	0.00
ATOM	687	N	THR	80	-4.794	-9.345	-12.850	0.00	0.00
ATOM	688	H	THR	80	-4.985	-9.175	-13.826	0.00	0.00
ATOM	689	CA	THR	80	-3.932	-8.380	-12.171	0.00	0.00
ATOM	690	CB	THR	80	-3.313	-7.404	-13.188	0.00	0.00
ATOM	691	CG2	THR	80	-2.263	-6.487	-12.550	0.00	0.00
ATOM	692	OG1	THR	80	-2.688	-8.125	-14.231	0.00	0.00
ATOM	693	HG1	THR	80	-2.352	-7.496	-14.876	0.00	0.00
ATOM	694	C	THR	80	-4.701	-7.631	-11.075	0.00	0.00
ATOM	695	O	THR	80	-4.208	-7.525	-9.951	0.00	0.00
ATOM	696	N	LEU	81	-5.914	-7.146	-11.381	0.00	0.00
ATOM	697	H	LEU	81	-6.254	-7.229	-12.330	0.00	0.00
ATOM	698	CA	LEU	81	-6.784	-6.508	-10.399	0.00	0.00
ATOM	699	CB	LEU	81	-7.852	-5.633	-11.088	0.00	0.00
ATOM	700	CG	LEU	81	-8.925	-6.361	-11.926	0.00	0.00
ATOM	701	CD1	LEU	81	-10.130	-6.825	-11.091	0.00	0.00
ATOM	702	CD2	LEU	81	-9.447	-5.431	-13.032	0.00	0.00
ATOM	703	C	LEU	81	-7.354	-7.502	-9.385	0.00	0.00
ATOM	704	O	LEU	81	-7.630	-7.100	-8.259	0.00	0.00
ATOM	705	N	CYS	82	-7.474	-8.790	-9.743	0.00	0.00

ATOM	706	H	CYS	82	-7.232	-9.060	-10.685	0.00	0.00
ATOM	707	CA	CYS	82	-7.870	-9.842	-8.815	0.00	0.00
ATOM	708	CB	CYS	82	-8.181	-11.122	-9.601	0.00	0.00
ATOM	709	SG	CYS	82	-8.822	-12.397	-8.483	0.00	0.00
ATOM	710	HG	CYS	82	-8.977	-13.342	-9.415	0.00	0.00
ATOM	711	C	CYS	82	-6.773	-10.071	-7.771	0.00	0.00
ATOM	712	O	CYS	82	-7.084	-10.069	-6.581	0.00	0.00
ATOM	713	N	ILE	83	-5.505	-10.239	-8.191	0.00	0.00
ATOM	714	H	ILE	83	-5.299	-10.228	-9.181	0.00	0.00
ATOM	715	CA	ILE	83	-4.407	-10.490	-7.258	0.00	0.00
ATOM	716	CB	ILE	83	-3.110	-11.018	-7.916	0.00	0.00
ATOM	717	CG2	ILE	83	-3.376	-12.398	-8.545	0.00	0.00
ATOM	718	CG1	ILE	83	-2.464	-10.029	-8.908	0.00	0.00
ATOM	719	CD1	ILE	83	-1.076	-10.449	-9.406	0.00	0.00
ATOM	720	C	ILE	83	-4.147	-9.303	-6.326	0.00	0.00
ATOM	721	O	ILE	83	-3.876	-9.520	-5.147	0.00	0.00
ATOM	722	N	SER	84	-4.295	-8.065	-6.815	0.00	0.00
ATOM	723	H	SER	84	-4.518	-7.952	-7.795	0.00	0.00
ATOM	724	CA	SER	84	-4.185	-6.861	-5.999	0.00	0.00
ATOM	725	CB	SER	84	-4.229	-5.644	-6.931	0.00	0.00
ATOM	726	OG	SER	84	-4.021	-4.452	-6.205	0.00	0.00
ATOM	727	HG	SER	84	-4.040	-3.713	-6.817	0.00	0.00
ATOM	728	C	SER	84	-5.305	-6.788	-4.952	0.00	0.00
ATOM	729	O	SER	84	-5.040	-6.413	-3.811	0.00	0.00
ATOM	730	N	VAL	85	-6.535	-7.178	-5.324	0.00	0.00
ATOM	731	H	VAL	85	-6.684	-7.476	-6.279	0.00	0.00
ATOM	732	CA	VAL	85	-7.690	-7.218	-4.428	0.00	0.00
ATOM	733	CB	VAL	85	-8.998	-7.352	-5.246	0.00	0.00
ATOM	734	CG1	VAL	85	-10.214	-7.827	-4.431	0.00	0.00
ATOM	735	CG2	VAL	85	-9.361	-5.986	-5.859	0.00	0.00
ATOM	736	C	VAL	85	-7.544	-8.290	-3.334	0.00	0.00
ATOM	737	O	VAL	85	-8.061	-8.092	-2.235	0.00	0.00
ATOM	738	N	LEU	86	-6.811	-9.385	-3.579	0.00	0.00
ATOM	739	H	LEU	86	-6.409	-9.519	-4.497	0.00	0.00
ATOM	740	CA	LEU	86	-6.530	-10.378	-2.544	0.00	0.00
ATOM	741	CB	LEU	86	-5.931	-11.656	-3.161	0.00	0.00
ATOM	742	CG	LEU	86	-6.917	-12.472	-4.025	0.00	0.00
ATOM	743	CD1	LEU	86	-6.158	-13.577	-4.772	0.00	0.00
ATOM	744	CD2	LEU	86	-8.036	-13.112	-3.188	0.00	0.00
ATOM	745	C	LEU	86	-5.603	-9.815	-1.462	0.00	0.00
ATOM	746	O	LEU	86	-5.867	-10.023	-0.277	0.00	0.00
ATOM	747	N	LEU	87	-4.555	-9.073	-1.855	0.00	0.00
ATOM	748	H	LEU	87	-4.386	-8.940	-2.843	0.00	0.00
ATOM	749	CA	LEU	87	-3.693	-8.366	-0.911	0.00	0.00
ATOM	750	CB	LEU	87	-2.393	-7.889	-1.592	0.00	0.00
ATOM	751	CG	LEU	87	-1.291	-8.950	-1.828	0.00	0.00
ATOM	752	CD1	LEU	87	-0.956	-9.769	-0.571	0.00	0.00
ATOM	753	CD2	LEU	87	-1.575	-9.897	-2.998	0.00	0.00
ATOM	754	C	LEU	87	-4.417	-7.191	-0.237	0.00	0.00
ATOM	755	O	LEU	87	-4.011	-6.796	0.855	0.00	0.00
ATOM	756	N	ALA	88	-5.496	-6.665	-0.837	0.00	0.00
ATOM	757	H	ALA	88	-5.776	-7.017	-1.742	0.00	0.00
ATOM	758	CA	ALA	88	-6.288	-5.590	-0.255	0.00	0.00
ATOM	759	CB	ALA	88	-7.211	-4.976	-1.305	0.00	0.00
ATOM	760	C	ALA	88	-7.083	-6.048	0.972	0.00	0.00
ATOM	761	O	ALA	88	-7.166	-5.302	1.946	0.00	0.00
ATOM	762	N	LEU	89	-7.629	-7.272	0.946	0.00	0.00
ATOM	763	H	LEU	89	-7.542	-7.830	0.106	0.00	0.00
ATOM	764	CA	LEU	89	-8.274	-7.881	2.106	0.00	0.00
ATOM	765	CB	LEU	89	-9.186	-9.043	1.662	0.00	0.00
ATOM	766	CG	LEU	89	-10.632	-8.658	1.276	0.00	0.00
ATOM	767	CD1	LEU	89	-11.423	-8.092	2.468	0.00	0.00
ATOM	768	CD2	LEU	89	-10.716	-7.689	0.089	0.00	0.00
ATOM	769	C	LEU	89	-7.245	-8.364	3.140	0.00	0.00
ATOM	770	O	LEU	89	-7.584	-8.432	4.321	0.00	0.00

ATOM	771	N	THR	90	-5.994	-8.643	2.734	0.00	0.00
ATOM	772	H	THR	90	-5.777	-8.588	1.748	0.00	0.00
ATOM	773	CA	THR	90	-4.900	-8.941	3.660	0.00	0.00
ATOM	774	CB	THR	90	-3.669	-9.491	2.901	0.00	0.00
ATOM	775	CG2	THR	90	-2.336	-8.768	3.142	0.00	0.00
ATOM	776	OG1	THR	90	-3.485	-10.845	3.257	0.00	0.00
ATOM	777	HG1	THR	90	-2.755	-11.198	2.741	0.00	0.00
ATOM	778	C	THR	90	-4.597	-7.729	4.565	0.00	0.00
ATOM	779	O	THR	90	-4.396	-7.880	5.770	0.00	0.00
ATOM	780	N	PHE	91	-4.622	-6.530	3.975	0.00	0.00
ATOM	781	H	PHE	91	-4.792	-6.522	2.979	0.00	0.00
ATOM	782	CA	PHE	91	-4.453	-5.213	4.589	0.00	0.00
ATOM	783	CB	PHE	91	-4.322	-4.228	3.394	0.00	0.00
ATOM	784	CG	PHE	91	-3.356	-3.056	3.460	0.00	0.00
ATOM	785	CD1	PHE	91	-2.423	-2.883	2.414	0.00	0.00
ATOM	786	CE1	PHE	91	-1.616	-1.734	2.355	0.00	0.00
ATOM	787	CZ	PHE	91	-1.734	-0.745	3.343	0.00	0.00
ATOM	788	CE2	PHE	91	-2.641	-0.920	4.401	0.00	0.00
ATOM	789	CD2	PHE	91	-3.457	-2.064	4.456	0.00	0.00
ATOM	790	C	PHE	91	-5.683	-4.789	5.417	0.00	0.00
ATOM	791	O	PHE	91	-5.598	-3.869	6.228	0.00	0.00
ATOM	792	N	PHE	92	-6.842	-5.423	5.194	0.00	0.00
ATOM	793	H	PHE	92	-6.868	-6.154	4.498	0.00	0.00
ATOM	794	CA	PHE	92	-8.094	-5.092	5.865	0.00	0.00
ATOM	795	CB	PHE	92	-9.244	-5.283	4.865	0.00	0.00
ATOM	796	CG	PHE	92	-10.588	-4.770	5.342	0.00	0.00
ATOM	797	CD1	PHE	92	-11.566	-5.666	5.815	0.00	0.00
ATOM	798	CE1	PHE	92	-12.813	-5.182	6.250	0.00	0.00
ATOM	799	CZ	PHE	92	-13.082	-3.802	6.223	0.00	0.00
ATOM	800	CE2	PHE	92	-12.107	-2.905	5.751	0.00	0.00
ATOM	801	CD2	PHE	92	-10.866	-3.390	5.305	0.00	0.00
ATOM	802	C	PHE	92	-8.318	-5.951	7.113	0.00	0.00
ATOM	803	O	PHE	92	-8.996	-5.514	8.038	0.00	0.00
ATOM	804	N	LEU	93	-7.720	-7.147	7.170	0.00	0.00
ATOM	805	H	LEU	93	-7.216	-7.478	6.358	0.00	0.00
ATOM	806	CA	LEU	93	-7.607	-7.931	8.393	0.00	0.00
ATOM	807	CB	LEU	93	-7.337	-9.401	8.029	0.00	0.00
ATOM	808	CG	LEU	93	-8.505	-10.093	7.292	0.00	0.00
ATOM	809	CD1	LEU	93	-8.049	-11.471	6.794	0.00	0.00
ATOM	810	CD2	LEU	93	-9.743	-10.260	8.187	0.00	0.00
ATOM	811	C	LEU	93	-6.476	-7.392	9.286	0.00	0.00
ATOM	812	O	LEU	93	-6.534	-7.605	10.495	0.00	0.00
ATOM	813	N	LEU	94	-5.492	-6.665	8.716	0.00	0.00
ATOM	814	H	LEU	94	-5.499	-6.553	7.712	0.00	0.00
ATOM	815	CA	LEU	94	-4.451	-5.952	9.457	0.00	0.00
ATOM	816	CB	LEU	94	-3.480	-5.226	8.501	0.00	0.00
ATOM	817	CG	LEU	94	-2.353	-4.352	9.118	0.00	0.00
ATOM	818	CD1	LEU	94	-1.439	-3.925	7.963	0.00	0.00
ATOM	819	CD2	LEU	94	-2.778	-3.049	9.821	0.00	0.00
ATOM	820	C	LEU	94	-5.090	-4.966	10.421	0.00	0.00
ATOM	821	O	LEU	94	-4.900	-5.085	11.631	0.00	0.00
ATOM	822	N	LEU	95	-5.820	-3.984	9.872	0.00	0.00
ATOM	823	H	LEU	95	-5.919	-3.951	8.867	0.00	0.00
ATOM	824	CA	LEU	95	-6.449	-2.929	10.650	0.00	0.00
ATOM	825	CB	LEU	95	-7.031	-1.860	9.702	0.00	0.00
ATOM	826	CG	LEU	95	-8.254	-2.255	8.847	0.00	0.00
ATOM	827	CD1	LEU	95	-9.593	-1.964	9.540	0.00	0.00
ATOM	828	CD2	LEU	95	-8.260	-1.499	7.512	0.00	0.00
ATOM	829	C	LEU	95	-7.493	-3.521	11.603	0.00	0.00
ATOM	830	O	LEU	95	-7.759	-2.920	12.628	0.00	0.00
ATOM	831	N	ILE	96	-8.050	-4.708	11.327	0.00	0.00
ATOM	832	H	ILE	96	-7.793	-5.180	10.472	0.00	0.00
ATOM	833	CA	ILE	96	-9.022	-5.369	12.197	0.00	0.00
ATOM	834	CB	ILE	96	-9.920	-6.295	11.322	0.00	0.00
ATOM	835	CG2	ILE	96	-10.612	-7.453	12.070	0.00	0.00

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ATOM    836  CG1 ILE    96     -10.979   -5.416   10.613  0.00  0.00
ATOM    837  CD1 ILE    96     -11.868   -6.145    9.597  0.00  0.00
ATOM    838  C   ILE    96      -8.387   -6.082   13.410  0.00  0.00
ATOM    839  O   ILE    96      -9.102   -6.439   14.344  0.00  0.00
ATOM    840  N   SER    97      -7.059   -6.234   13.455  0.00  0.00
ATOM    841  H   SER    97      -6.507   -5.963   12.651  0.00  0.00
ATOM    842  CA  SER    97      -6.334   -6.780   14.606  0.00  0.00
ATOM    843  CB  SER    97      -5.760   -8.160   14.256  0.00  0.00
ATOM    844  OG  SER    97      -5.015   -8.132   13.060  0.00  0.00
ATOM    845  HG  SER    97      -4.783   -9.033   12.822  0.00  0.00
ATOM    846  C   SER    97      -5.306   -5.798   15.185  0.00  0.00
ATOM    847  O   SER    97      -4.693   -6.100   16.208  0.00  0.00
ATOM    848  N   LYS    98      -5.198   -4.596   14.597  0.00  0.00
ATOM    849  H   LYS    98      -5.681   -4.458   13.721  0.00  0.00
ATOM    850  CA  LYS    98      -4.651   -3.399   15.233  0.00  0.00
ATOM    851  CB  LYS    98      -3.647   -2.714   14.287  0.00  0.00
ATOM    852  CG  LYS    98      -2.211   -3.185   14.574  0.00  0.00
ATOM    853  CD  LYS    98      -1.468   -2.332   15.616  0.00  0.00
ATOM    854  CE  LYS    98      -2.219   -2.091   16.926  0.00  0.00
ATOM    855  NZ  LYS    98      -1.576   -1.033   17.722  0.00  0.00
ATOM    856  HZ1 LYS    98      -1.606   -0.172   17.188  0.00  0.00
ATOM    857  HZ2 LYS    98      -2.081   -0.902   18.587  0.00  0.00
ATOM    858  HZ3 LYS    98      -0.617   -1.281   17.915  0.00  0.00
ATOM    859  C   LYS    98      -5.757   -2.436   15.696  0.00  0.00
ATOM    860  O   LYS    98      -5.464   -1.551   16.499  0.00  0.00
ATOM    861  N   ILE    99      -7.014   -2.629   15.257  0.00  0.00
ATOM    862  H   ILE    99      -7.181   -3.351   14.572  0.00  0.00
ATOM    863  CA  ILE    99      -8.183   -1.910   15.761  0.00  0.00
ATOM    864  CB  ILE    99      -8.578   -0.611   14.993  0.00  0.00
ATOM    865  CG2 ILE    99      -7.440   -0.024   14.128  0.00  0.00
ATOM    866  CG1 ILE    99      -9.986   -0.568   14.330  0.00  0.00
ATOM    867  CD1 ILE    99     -10.151   -1.102   12.907  0.00  0.00
ATOM    868  C   ILE    99      -9.354   -2.838   16.111  0.00  0.00
ATOM    869  O   ILE    99      -9.812   -2.824   17.253  0.00  0.00
ATOM    870  N   NME   100      -9.856   -3.612   15.142  0.00  0.00
ATOM    871  H   NME   100      -9.425   -3.578   14.228  0.00  0.00
ATOM    872  CA  NME   100     -11.085   -4.380   15.281  0.00  0.00
TER
ATOM    873  CA  ACE   101       7.905   -7.165  -18.677  0.00  0.00
ATOM    874  C   ACE   101       7.125   -7.203  -17.370  0.00  0.00
ATOM    875  O   ACE   101       7.723   -7.240  -16.295  0.00  0.00
ATOM    876  N   GLU   102       5.788   -7.211  -17.481  0.00  0.00
ATOM    877  H   GLU   102       5.386   -7.173  -18.406  0.00  0.00
ATOM    878  CA  GLU   102       4.848   -7.189  -16.356  0.00  0.00
ATOM    879  CB  GLU   102       3.417   -7.059  -16.912  0.00  0.00
ATOM    880  CG  GLU   102       2.315   -6.884  -15.850  0.00  0.00
ATOM    881  CD  GLU   102       2.611   -5.777  -14.830  0.00  0.00
ATOM    882  OE1 GLU   102       2.451   -6.055  -13.621  0.00  0.00
ATOM    883  OE2 GLU   102       3.004   -4.674  -15.270  0.00  0.00
ATOM    884  C   GLU   102       4.997   -8.397  -15.412  0.00  0.00
ATOM    885  O   GLU   102       4.547   -8.337  -14.272  0.00  0.00
ATOM    886  N   LYS   103       5.656   -9.477  -15.853  0.00  0.00
ATOM    887  H   LYS   103       6.027   -9.457  -16.791  0.00  0.00
ATOM    888  CA  LYS   103       5.855  -10.692  -15.071  0.00  0.00
ATOM    889  CB  LYS   103       6.292  -11.843  -15.997  0.00  0.00
ATOM    890  CG  LYS   103       5.142  -12.514  -16.771  0.00  0.00
ATOM    891  CD  LYS   103       4.455  -11.619  -17.817  0.00  0.00
ATOM    892  CE  LYS   103       3.415  -12.388  -18.642  0.00  0.00
ATOM    893  NZ  LYS   103       4.035  -13.385  -19.536  0.00  0.00
ATOM    894  HZ1 LYS   103       4.552  -14.058  -18.988  0.00  0.00
ATOM    895  HZ2 LYS   103       3.316  -13.863  -20.062  0.00  0.00
ATOM    896  HZ3 LYS   103       4.664  -12.922  -20.177  0.00  0.00
ATOM    897  C   LYS   103       6.870  -10.507  -13.939  0.00  0.00
ATOM    898  O   LYS   103       6.650  -11.020  -12.842  0.00  0.00
ATOM    899  N   MET   104       7.961   -9.768  -14.185  0.00  0.00
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ATOM	900	H	MET	104	8.084	-9.368	-15.104	0.00	0.00
ATOM	901	CA	MET	104	8.896	-9.366	-13.138	0.00	0.00
ATOM	902	CB	MET	104	10.229	-8.957	-13.787	0.00	0.00
ATOM	903	CG	MET	104	11.329	-8.633	-12.766	0.00	0.00
ATOM	904	SD	MET	104	11.730	-9.976	-11.612	0.00	0.00
ATOM	905	CE	MET	104	13.090	-9.197	-10.705	0.00	0.00
ATOM	906	C	MET	104	8.305	-8.224	-12.304	0.00	0.00
ATOM	907	O	MET	104	8.615	-8.137	-11.120	0.00	0.00
ATOM	908	N	THR	105	7.436	-7.383	-12.888	0.00	0.00
ATOM	909	H	THR	105	7.231	-7.492	-13.872	0.00	0.00
ATOM	910	CA	THR	105	6.771	-6.285	-12.189	0.00	0.00
ATOM	911	CB	THR	105	5.997	-5.394	-13.179	0.00	0.00
ATOM	912	CG2	THR	105	5.397	-4.156	-12.502	0.00	0.00
ATOM	913	OG1	THR	105	6.855	-4.945	-14.208	0.00	0.00
ATOM	914	HG1	THR	105	6.350	-4.365	-14.783	0.00	0.00
ATOM	915	C	THR	105	5.844	-6.813	-11.088	0.00	0.00
ATOM	916	O	THR	105	5.914	-6.335	-9.955	0.00	0.00
ATOM	917	N	LEU	106	4.997	-7.805	-11.402	0.00	0.00
ATOM	918	H	LEU	106	4.955	-8.138	-12.357	0.00	0.00
ATOM	919	CA	LEU	106	4.120	-8.434	-10.420	0.00	0.00
ATOM	920	CB	LEU	106	2.946	-9.161	-11.107	0.00	0.00
ATOM	921	CG	LEU	106	3.285	-10.405	-11.958	0.00	0.00
ATOM	922	CD1	LEU	106	3.360	-11.700	-11.133	0.00	0.00
ATOM	923	CD2	LEU	106	2.220	-10.598	-13.048	0.00	0.00
ATOM	924	C	LEU	106	4.886	-9.297	-9.415	0.00	0.00
ATOM	925	O	LEU	106	4.414	-9.452	-8.293	0.00	0.00
ATOM	926	N	CYS	107	6.076	-9.802	-9.775	0.00	0.00
ATOM	927	H	CYS	107	6.410	-9.644	-10.715	0.00	0.00
ATOM	928	CA	CYS	107	6.959	-10.502	-8.851	0.00	0.00
ATOM	929	CB	CYS	107	8.082	-11.186	-9.642	0.00	0.00
ATOM	930	SG	CYS	107	9.106	-12.185	-8.530	0.00	0.00
ATOM	931	HG	CYS	107	9.956	-12.618	-9.466	0.00	0.00
ATOM	932	C	CYS	107	7.514	-9.531	-7.807	0.00	0.00
ATOM	933	O	CYS	107	7.409	-9.826	-6.618	0.00	0.00
ATOM	934	N	ILE	108	8.071	-8.379	-8.226	0.00	0.00
ATOM	935	H	ILE	108	8.128	-8.179	-9.216	0.00	0.00
ATOM	936	CA	ILE	108	8.642	-7.413	-7.290	0.00	0.00
ATOM	937	CB	ILE	108	9.539	-6.330	-7.938	0.00	0.00
ATOM	938	CG2	ILE	108	10.773	-6.998	-8.571	0.00	0.00
ATOM	939	CG1	ILE	108	8.800	-5.405	-8.926	0.00	0.00
ATOM	940	CD1	ILE	108	9.621	-4.198	-9.395	0.00	0.00
ATOM	941	C	ILE	108	7.585	-6.825	-6.352	0.00	0.00
ATOM	942	O	ILE	108	7.856	-6.698	-5.162	0.00	0.00
ATOM	943	N	SER	109	6.372	-6.546	-6.845	0.00	0.00
ATOM	944	H	SER	109	6.205	-6.679	-7.834	0.00	0.00
ATOM	945	CA	SER	109	5.265	-6.074	-6.021	0.00	0.00
ATOM	946	CB	SER	109	4.092	-5.731	-6.947	0.00	0.00
ATOM	947	OG	SER	109	3.028	-5.162	-6.216	0.00	0.00
ATOM	948	HG	SER	109	2.317	-4.947	-6.824	0.00	0.00
ATOM	949	C	SER	109	4.848	-7.120	-4.978	0.00	0.00
ATOM	950	O	SER	109	4.563	-6.754	-3.839	0.00	0.00
ATOM	951	N	VAL	110	4.849	-8.412	-5.349	0.00	0.00
ATOM	952	H	VAL	110	5.095	-8.644	-6.301	0.00	0.00
ATOM	953	CA	VAL	110	4.526	-9.523	-4.455	0.00	0.00
ATOM	954	CB	VAL	110	4.228	-10.801	-5.279	0.00	0.00
ATOM	955	CG1	VAL	110	4.290	-12.110	-4.473	0.00	0.00
ATOM	956	CG2	VAL	110	2.814	-10.701	-5.883	0.00	0.00
ATOM	957	C	VAL	110	5.595	-9.736	-3.370	0.00	0.00
ATOM	958	O	VAL	110	5.249	-10.185	-2.278	0.00	0.00
ATOM	959	N	LEU	111	6.864	-9.373	-3.610	0.00	0.00
ATOM	960	H	LEU	111	7.116	-9.015	-4.521	0.00	0.00
ATOM	961	CA	LEU	111	7.889	-9.415	-2.568	0.00	0.00
ATOM	962	CB	LEU	111	9.294	-9.189	-3.157	0.00	0.00
ATOM	963	CG	LEU	111	9.802	-10.327	-4.068	0.00	0.00
ATOM	964	CD1	LEU	111	11.103	-9.891	-4.757	0.00	0.00

ATOM	965	CD2	LEU	111	10.057	-11.628	-3.292	0.00	0.00
ATOM	966	C	LEU	111	7.591	-8.396	-1.466	0.00	0.00
ATOM	967	O	LEU	111	7.632	-8.750	-0.288	0.00	0.00
ATOM	968	N	LEU	112	7.252	-7.156	-1.847	0.00	0.00
ATOM	969	H	LEU	112	7.233	-6.937	-2.834	0.00	0.00
ATOM	970	CA	LEU	112	6.854	-6.108	-0.913	0.00	0.00
ATOM	971	CB	LEU	112	6.958	-4.728	-1.587	0.00	0.00
ATOM	972	CG	LEU	112	8.387	-4.206	-1.871	0.00	0.00
ATOM	973	CD1	LEU	112	9.353	-4.393	-0.688	0.00	0.00
ATOM	974	CD2	LEU	112	9.042	-4.756	-3.139	0.00	0.00
ATOM	975	C	LEU	112	5.460	-6.346	-0.311	0.00	0.00
ATOM	976	O	LEU	112	5.132	-5.721	0.698	0.00	0.00
ATOM	977	N	ALA	113	4.666	-7.274	-0.866	0.00	0.00
ATOM	978	H	ALA	113	4.973	-7.744	-1.706	0.00	0.00
ATOM	979	CA	ALA	113	3.404	-7.696	-0.277	0.00	0.00
ATOM	980	CB	ALA	113	2.547	-8.426	-1.311	0.00	0.00
ATOM	981	C	ALA	113	3.618	-8.559	0.969	0.00	0.00
ATOM	982	O	ALA	113	2.930	-8.356	1.969	0.00	0.00
ATOM	983	N	LEU	114	4.583	-9.491	0.927	0.00	0.00
ATOM	984	H	LEU	114	5.105	-9.614	0.070	0.00	0.00
ATOM	985	CA	LEU	114	4.974	-10.298	2.081	0.00	0.00
ATOM	986	CB	LEU	114	5.771	-11.536	1.621	0.00	0.00
ATOM	987	CG	LEU	114	4.931	-12.778	1.245	0.00	0.00
ATOM	988	CD1	LEU	114	4.166	-13.350	2.450	0.00	0.00
ATOM	989	CD2	LEU	114	3.961	-12.538	0.081	0.00	0.00
ATOM	990	C	LEU	114	5.779	-9.482	3.103	0.00	0.00
ATOM	991	O	LEU	114	5.748	-9.823	4.285	0.00	0.00
ATOM	992	N	THR	115	6.437	-8.388	2.684	0.00	0.00
ATOM	993	H	THR	115	6.462	-8.179	1.695	0.00	0.00
ATOM	994	CA	THR	115	7.061	-7.429	3.597	0.00	0.00
ATOM	995	CB	THR	115	7.850	-6.357	2.822	0.00	0.00
ATOM	996	CG2	THR	115	8.536	-5.343	3.744	0.00	0.00
ATOM	997	OG1	THR	115	8.856	-6.976	2.049	0.00	0.00
ATOM	998	HG1	THR	115	9.358	-6.292	1.600	0.00	0.00
ATOM	999	C	THR	115	6.004	-6.808	4.520	0.00	0.00
ATOM	1000	O	THR	115	6.203	-6.724	5.732	0.00	0.00
ATOM	1001	N	PHE	116	4.865	-6.420	3.937	0.00	0.00
ATOM	1002	H	PHE	116	4.787	-6.534	2.935	0.00	0.00
ATOM	1003	CA	PHE	116	3.714	-5.834	4.610	0.00	0.00
ATOM	1004	CB	PHE	116	2.906	-5.115	3.515	0.00	0.00
ATOM	1005	CG	PHE	116	1.976	-4.054	4.050	0.00	0.00
ATOM	1006	CD1	PHE	116	2.473	-2.763	4.304	0.00	0.00
ATOM	1007	CE1	PHE	116	1.655	-1.804	4.920	0.00	0.00
ATOM	1008	CZ	PHE	116	0.337	-2.137	5.275	0.00	0.00
ATOM	1009	CE2	PHE	116	-0.178	-3.405	4.957	0.00	0.00
ATOM	1010	CD2	PHE	116	0.638	-4.365	4.345	0.00	0.00
ATOM	1011	C	PHE	116	2.840	-6.870	5.349	0.00	0.00
ATOM	1012	O	PHE	116	1.930	-6.491	6.087	0.00	0.00
ATOM	1013	N	PHE	117	3.110	-8.171	5.174	0.00	0.00
ATOM	1014	H	PHE	117	3.853	-8.430	4.541	0.00	0.00
ATOM	1015	CA	PHE	117	2.400	-9.253	5.851	0.00	0.00
ATOM	1016	CB	PHE	117	2.221	-10.413	4.862	0.00	0.00
ATOM	1017	CG	PHE	117	1.273	-11.497	5.337	0.00	0.00
ATOM	1018	CD1	PHE	117	1.772	-12.711	5.847	0.00	0.00
ATOM	1019	CE1	PHE	117	0.881	-13.709	6.281	0.00	0.00
ATOM	1020	CZ	PHE	117	-0.507	-13.495	6.215	0.00	0.00
ATOM	1021	CE2	PHE	117	-1.006	-12.283	5.705	0.00	0.00
ATOM	1022	CD2	PHE	117	-0.117	-11.289	5.264	0.00	0.00
ATOM	1023	C	PHE	117	3.141	-9.726	7.108	0.00	0.00
ATOM	1024	O	PHE	117	2.504	-10.191	8.048	0.00	0.00
ATOM	1025	N	LEU	118	4.470	-9.571	7.159	0.00	0.00
ATOM	1026	H	LEU	118	4.952	-9.227	6.340	0.00	0.00
ATOM	1027	CA	LEU	118	5.248	-9.706	8.388	0.00	0.00
ATOM	1028	CB	LEU	118	6.733	-9.887	8.025	0.00	0.00
ATOM	1029	CG	LEU	118	7.045	-11.202	7.277	0.00	0.00

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ATOM   1030  CD1 LEU   118       8.486 -11.161   6.750  0.00  0.00
ATOM   1031  CD2 LEU   118       6.867 -12.436   8.174  0.00  0.00
ATOM   1032  C   LEU   118       5.076  -8.470   9.290  0.00  0.00
ATOM   1033  O   LEU   118       5.266  -8.568  10.503  0.00  0.00
ATOM   1034  N   LEU   119       4.684  -7.327   8.702  0.00  0.00
ATOM   1035  H   LEU   119       4.577  -7.325   7.698  0.00  0.00
ATOM   1036  CA  LEU   119       4.344  -6.095   9.399  0.00  0.00
ATOM   1037  CB  LEU   119       4.091  -4.980   8.368  0.00  0.00
ATOM   1038  CG  LEU   119       3.542  -3.613   8.849  0.00  0.00
ATOM   1039  CD1 LEU   119       3.637  -2.659   7.650  0.00  0.00
ATOM   1040  CD2 LEU   119       2.071  -3.607   9.296  0.00  0.00
ATOM   1041  C   LEU   119       3.168  -6.312  10.329  0.00  0.00
ATOM   1042  O   LEU   119       3.315  -6.088  11.531  0.00  0.00
ATOM   1043  N   LEU   120       2.020  -6.742   9.780  0.00  0.00
ATOM   1044  H   LEU   120       1.965  -6.893   8.783  0.00  0.00
ATOM   1045  CA  LEU   120       0.847  -7.006  10.594  0.00  0.00
ATOM   1046  CB  LEU   120      -0.389  -7.303   9.718  0.00  0.00
ATOM   1047  CG  LEU   120      -0.420  -8.605   8.891  0.00  0.00
ATOM   1048  CD1 LEU   120      -1.031  -9.789   9.656  0.00  0.00
ATOM   1049  CD2 LEU   120      -1.238  -8.408   7.606  0.00  0.00
ATOM   1050  C   LEU   120       1.196  -8.082  11.617  0.00  0.00
ATOM   1051  O   LEU   120       0.868  -7.887  12.770  0.00  0.00
ATOM   1052  N   ILE   121       1.952  -9.132  11.261  0.00  0.00
ATOM   1053  H   ILE   121       2.237  -9.221  10.296  0.00  0.00
ATOM   1054  CA  ILE   121       2.309 -10.226  12.171  0.00  0.00
ATOM   1055  CB  ILE   121       3.044 -11.338  11.371  0.00  0.00
ATOM   1056  CG2 ILE   121       3.910 -12.280  12.235  0.00  0.00
ATOM   1057  CG1 ILE   121       1.996 -12.159  10.582  0.00  0.00
ATOM   1058  CD1 ILE   121       2.583 -13.151   9.570  0.00  0.00
ATOM   1059  C   ILE   121       3.063  -9.794  13.437  0.00  0.00
ATOM   1060  O   ILE   121       2.951 -10.474  14.455  0.00  0.00
ATOM   1061  N   SER   122       3.779  -8.666  13.408  0.00  0.00
ATOM   1062  H   SER   122       3.814  -8.140  12.545  0.00  0.00
ATOM   1063  CA  SER   122       4.547  -8.154  14.544  0.00  0.00
ATOM   1064  CB  SER   122       5.983  -7.919  14.082  0.00  0.00
ATOM   1065  OG  SER   122       6.054  -6.966  13.038  0.00  0.00
ATOM   1066  HG  SER   122       5.710  -7.367  12.233  0.00  0.00
ATOM   1067  C   SER   122       3.910  -6.923  15.201  0.00  0.00
ATOM   1068  O   SER   122       4.356  -6.504  16.269  0.00  0.00
ATOM   1069  N   LYS   123       2.824  -6.407  14.610  0.00  0.00
ATOM   1070  H   LYS   123       2.554  -6.785  13.712  0.00  0.00
ATOM   1071  CA  LYS   123       1.865  -5.507  15.238  0.00  0.00
ATOM   1072  CB  LYS   123       1.524  -4.373  14.258  0.00  0.00
ATOM   1073  CG  LYS   123       2.444  -3.153  14.412  0.00  0.00
ATOM   1074  CD  LYS   123       2.457  -2.557  15.837  0.00  0.00
ATOM   1075  CE  LYS   123       3.740  -2.934  16.588  0.00  0.00
ATOM   1076  NZ  LYS   123       3.804  -2.279  17.906  0.00  0.00
ATOM   1077  HZ1 LYS   123       3.039  -2.591  18.485  0.00  0.00
ATOM   1078  HZ2 LYS   123       4.684  -2.505  18.349  0.00  0.00
ATOM   1079  HZ3 LYS   123       3.755  -1.276  17.784  0.00  0.00
ATOM   1080  C   LYS   123       0.606  -6.239  15.731  0.00  0.00
ATOM   1081  O   LYS   123      -0.209  -5.615  16.411  0.00  0.00
ATOM   1082  N   ILE   124       0.460  -7.540  15.426  0.00  0.00
ATOM   1083  H   ILE   124       1.160  -7.964  14.834  0.00  0.00
ATOM   1084  CA  ILE   124      -0.713  -8.357  15.735  0.00  0.00
ATOM   1085  CB  ILE   124      -1.737  -8.470  14.570  0.00  0.00
ATOM   1086  CG2 ILE   124      -2.030  -7.099  13.925  0.00  0.00
ATOM   1087  CG1 ILE   124      -1.402  -9.547  13.510  0.00  0.00
ATOM   1088  CD1 ILE   124      -2.384 -10.723  13.496  0.00  0.00
ATOM   1089  C   ILE   124      -0.378  -9.710  16.388  0.00  0.00
ATOM   1090  O   ILE   124      -1.293 -10.446  16.758  0.00  0.00
ATOM   1091  N   NME   125       0.912 -10.026  16.573  0.00  0.00
ATOM   1092  H   NME   125       1.620  -9.385  16.248  0.00  0.00
ATOM   1093  CA  NME   125       1.375 -11.257  17.196  0.00  0.00
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END

Appendix 5: Atomic Coordinates of the Luminal Channel of a **α3β2 nAChR** Ion Channel

pdb file of the α3β2 model

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REMARK    File generated by Swiss-PdbViewer  3.70b0
ATOM      1  N   GLU     2       8.656   3.377 -17.484  0.00  0.00
ATOM      2  CA  GLU     2       8.345   2.482 -16.365  0.00  0.00
ATOM      3  C   GLU     2       9.541   2.246 -15.422  0.00  0.00
ATOM      4  O   GLU     2       9.344   1.832 -14.284  0.00  0.00
ATOM      5  CB  GLU     2       7.781   1.164 -16.930  0.00  0.00
ATOM      6  CG  GLU     2       7.274   0.164 -15.874  0.00  0.00
ATOM      7  CD  GLU     2       6.311   0.782 -14.852  0.00  0.00
ATOM      8  OE1 GLU     2       6.525   0.540 -13.643  0.00  0.00
ATOM      9  OE2 GLU     2       5.381   1.495 -15.291  0.00  0.00
ATOM     10  H   GLU     2       8.496   3.014 -18.412  1.00 99.99
ATOM     11  N   LYS     3      10.771   2.539 -15.863  0.00  0.00
ATOM     12  CA  LYS     3      11.990   2.351 -15.083  0.00  0.00
ATOM     13  C   LYS     3      12.132   3.373 -13.949  0.00  0.00
ATOM     14  O   LYS     3      12.566   3.010 -12.857  0.00  0.00
ATOM     15  CB  LYS     3      13.218   2.415 -16.010  0.00  0.00
ATOM     16  CG  LYS     3      13.496   1.120 -16.797  0.00  0.00
ATOM     17  CD  LYS     3      12.434   0.760 -17.851  0.00  0.00
ATOM     18  CE  LYS     3      12.843  -0.456 -18.690  0.00  0.00
ATOM     19  NZ  LYS     3      13.984  -0.166 -19.580  0.00  0.00
ATOM     20  H   LYS     3      10.867   2.901 -16.800  1.00 99.99
ATOM     21  HZ1 LYS     3      14.784   0.109 -19.027  1.00 99.99
ATOM     22  HZ2 LYS     3      14.216  -0.990 -20.116  1.00 99.99
ATOM     23  HZ3 LYS     3      13.741   0.585 -20.211  1.00 99.99
ATOM     24  N   VAL     4      11.753   4.634 -14.194  0.00  0.00
ATOM     25  CA  VAL     4      11.662   5.664 -13.159  0.00  0.00
ATOM     26  C   VAL     4      10.413   5.416 -12.307  0.00  0.00
ATOM     27  O   VAL     4      10.455   5.677 -11.110  0.00  0.00
ATOM     28  CB  VAL     4      11.627   7.065 -13.814  0.00  0.00
ATOM     29  CG1 VAL     4      11.499   8.186 -12.768  0.00  0.00
ATOM     30  CG2 VAL     4      12.901   7.325 -14.639  0.00  0.00
ATOM     31  H   VAL     4      11.400   4.864 -15.112  1.00 99.99
ATOM     32  N   THR     5       9.329   4.884 -12.897  0.00  0.00
ATOM     33  CA  THR     5       8.083   4.583 -12.195  0.00  0.00
ATOM     34  C   THR     5       8.300   3.535 -11.096  0.00  0.00
ATOM     35  O   THR     5       7.868   3.747  -9.963  0.00  0.00
ATOM     36  CB  THR     5       6.994   4.125 -13.184  0.00  0.00
ATOM     37  OG1 THR     5       6.830   5.082 -14.210  0.00  0.00
ATOM     38  CG2 THR     5       5.633   3.934 -12.505  0.00  0.00
ATOM     39  H   THR     5       9.350   4.704 -13.891  1.00 99.99
ATOM     40  HG1 THR     5       6.121   4.783 -14.784  1.00 99.99
ATOM     41  N   LEU     6       8.984   2.425 -11.414  0.00  0.00
ATOM     42  CA  LEU     6       9.311   1.394 -10.436  0.00  0.00
ATOM     43  C   LEU     6      10.367   1.852  -9.428  0.00  0.00
ATOM     44  O   LEU     6      10.366   1.351  -8.308  0.00  0.00
ATOM     45  CB  LEU     6       9.642   0.056 -11.127  0.00  0.00
ATOM     46  CG  LEU     6      10.932  -0.001 -11.976  0.00  0.00
ATOM     47  CD1 LEU     6      12.185  -0.332 -11.150  0.00  0.00
ATOM     48  CD2 LEU     6      10.789  -1.070 -13.070  0.00  0.00
ATOM     49  H   LEU     6       9.287   2.286 -12.369  1.00 99.99
ATOM     50  N   CYS     7      11.216   2.830  -9.782  0.00  0.00
ATOM     51  CA  CYS     7      12.155   3.443  -8.852  0.00  0.00
ATOM     52  C   CYS     7      11.403   4.271  -7.805  0.00  0.00
ATOM     53  O   CYS     7      11.653   4.083  -6.616  0.00  0.00
ATOM     54  CB  CYS     7      13.169   4.290  -9.630  0.00  0.00
ATOM     55  SG  CYS     7      14.449   4.908  -8.504  0.00  0.00
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ATOM	56	H	CYS	7	11.170	3.204	-10.719	1.00	99.99
ATOM	57	HG	CYS	7	15.153	5.565	-9.430	1.00	99.99
ATOM	58	N	ILE	8	10.477	5.155	-8.222	0.00	0.00
ATOM	59	CA	ILE	8	9.741	6.010	-7.292	0.00	0.00
ATOM	60	C	ILE	8	8.822	5.213	-6.360	0.00	0.00
ATOM	61	O	ILE	8	8.715	5.561	-5.187	0.00	0.00
ATOM	62	CB	ILE	8	9.018	7.206	-7.957	0.00	0.00
ATOM	63	CG1	ILE	8	7.912	6.794	-8.950	0.00	0.00
ATOM	64	CG2	ILE	8	10.056	8.149	-8.595	0.00	0.00
ATOM	65	CD1	ILE	8	7.033	7.955	-9.431	0.00	0.00
ATOM	66	H	ILE	8	10.302	5.265	-9.212	1.00	99.99
ATOM	67	N	SER	9	8.223	4.116	-6.842	0.00	0.00
ATOM	68	CA	SER	9	7.430	3.207	-6.022	0.00	0.00
ATOM	69	C	SER	9	8.299	2.487	-4.981	0.00	0.00
ATOM	70	O	SER	9	7.865	2.322	-3.841	0.00	0.00
ATOM	71	CB	SER	9	6.746	2.198	-6.952	0.00	0.00
ATOM	72	OG	SER	9	5.880	1.355	-6.222	0.00	0.00
ATOM	73	H	SER	9	8.348	3.884	-7.819	1.00	99.99
ATOM	74	HG	SER	9	5.455	0.749	-6.834	1.00	99.99
ATOM	75	N	VAL	10	9.527	2.092	-5.355	0.00	0.00
ATOM	76	CA	VAL	10	10.488	1.439	-4.467	0.00	0.00
ATOM	77	C	VAL	10	11.045	2.397	-3.397	0.00	0.00
ATOM	78	O	VAL	10	11.425	1.934	-2.323	0.00	0.00
ATOM	79	CB	VAL	10	11.590	0.739	-5.301	0.00	0.00
ATOM	80	CG1	VAL	10	12.857	0.370	-4.510	0.00	0.00
ATOM	81	CG2	VAL	10	11.028	-0.564	-5.898	0.00	0.00
ATOM	82	H	VAL	10	9.822	2.259	-6.308	1.00	99.99
ATOM	83	N	LEU	11	11.046	3.718	-3.626	0.00	0.00
ATOM	84	CA	LEU	11	11.403	4.680	-2.585	0.00	0.00
ATOM	85	C	LEU	11	10.331	4.735	-1.493	0.00	0.00
ATOM	86	O	LEU	11	10.673	4.708	-0.310	0.00	0.00
ATOM	87	CB	LEU	11	11.629	6.081	-3.186	0.00	0.00
ATOM	88	CG	LEU	11	12.881	6.204	-4.080	0.00	0.00
ATOM	89	CD1	LEU	11	12.881	7.571	-4.779	0.00	0.00
ATOM	90	CD2	LEU	11	14.187	6.047	-3.287	0.00	0.00
ATOM	91	H	LEU	11	10.741	4.069	-4.523	1.00	99.99
ATOM	92	N	LEU	12	9.046	4.773	-1.879	0.00	0.00
ATOM	93	CA	LEU	12	7.933	4.712	-0.936	0.00	0.00
ATOM	94	C	LEU	12	7.813	3.333	-0.273	0.00	0.00
ATOM	95	O	LEU	12	7.270	3.253	0.827	0.00	0.00
ATOM	96	CB	LEU	12	6.609	5.114	-1.618	0.00	0.00
ATOM	97	CG	LEU	12	6.349	6.629	-1.800	0.00	0.00
ATOM	98	CD1	LEU	12	6.475	7.424	-0.490	0.00	0.00
ATOM	99	CD2	LEU	12	7.205	7.290	-2.885	0.00	0.00
ATOM	100	H	LEU	12	8.829	4.798	-2.866	1.00	99.99
ATOM	101	N	SER	13	8.359	2.271	-0.884	0.00	0.00
ATOM	102	CA	SER	13	8.421	0.946	-0.280	0.00	0.00
ATOM	103	C	SER	13	9.273	0.950	0.990	0.00	0.00
ATOM	104	O	SER	13	8.819	0.466	2.026	0.00	0.00
ATOM	105	CB	SER	13	8.951	-0.077	-1.282	0.00	0.00
ATOM	106	OG	SER	13	9.099	-1.310	-0.623	0.00	0.00
ATOM	107	H	SER	13	8.775	2.394	-1.797	1.00	99.99
ATOM	108	HG	SER	13	9.427	-1.956	-1.252	1.00	99.99
ATOM	109	N	LEU	14	10.492	1.503	0.918	0.00	0.00
ATOM	110	CA	LEU	14	11.374	1.623	2.074	0.00	0.00
ATOM	111	C	LEU	14	10.837	2.631	3.101	0.00	0.00
ATOM	112	O	LEU	14	11.157	2.497	4.282	0.00	0.00
ATOM	113	CB	LEU	14	12.797	2.007	1.620	0.00	0.00
ATOM	114	CG	LEU	14	13.726	0.831	1.239	0.00	0.00
ATOM	115	CD1	LEU	14	14.038	-0.075	2.441	0.00	0.00
ATOM	116	CD2	LEU	14	13.201	-0.019	0.073	0.00	0.00
ATOM	117	H	LEU	14	10.813	1.877	0.035	1.00	99.99
ATOM	118	N	THR	15	9.988	3.588	2.690	0.00	0.00
ATOM	119	CA	THR	15	9.285	4.477	3.614	0.00	0.00
ATOM	120	C	THR	15	8.292	3.705	4.503	0.00	0.00

ATOM	121	O	THR	15	8.154	4.016	5.685	0.00	0.00
ATOM	122	CB	THR	15	8.678	5.685	2.862	0.00	0.00
ATOM	123	OG1	THR	15	9.358	6.857	3.261	0.00	0.00
ATOM	124	CG2	THR	15	7.178	5.937	3.069	0.00	0.00
ATOM	125	H	THR	15	9.772	3.661	1.705	1.00	99.99
ATOM	126	HG1	THR	15	9.005	7.597	2.762	1.00	99.99
ATOM	127	N	VAL	16	7.654	2.667	3.948	0.00	0.00
ATOM	128	CA	VAL	16	6.734	1.752	4.625	0.00	0.00
ATOM	129	C	VAL	16	7.478	0.592	5.321	0.00	0.00
ATOM	130	O	VAL	16	6.869	-0.166	6.077	0.00	0.00
ATOM	131	CB	VAL	16	5.717	1.249	3.563	0.00	0.00
ATOM	132	CG1	VAL	16	4.800	0.106	4.030	0.00	0.00
ATOM	133	CG2	VAL	16	4.835	2.427	3.122	0.00	0.00
ATOM	134	H	VAL	16	7.830	2.479	2.969	1.00	99.99
ATOM	135	N	PHE	17	8.795	0.456	5.118	0.00	0.00
ATOM	136	CA	PHE	17	9.611	-0.530	5.817	0.00	0.00
ATOM	137	C	PHE	17	10.230	0.041	7.098	0.00	0.00
ATOM	138	O	PHE	17	10.403	-0.691	8.068	0.00	0.00
ATOM	139	CB	PHE	17	10.708	-1.033	4.870	0.00	0.00
ATOM	140	CG	PHE	17	11.522	-2.193	5.415	0.00	0.00
ATOM	141	CD1	PHE	17	12.914	-2.068	5.585	0.00	0.00
ATOM	142	CD2	PHE	17	10.886	-3.405	5.750	0.00	0.00
ATOM	143	CE1	PHE	17	13.666	-3.150	6.076	0.00	0.00
ATOM	144	CE2	PHE	17	11.637	-4.484	6.249	0.00	0.00
ATOM	145	CZ	PHE	17	13.028	-4.358	6.409	0.00	0.00
ATOM	146	H	PHE	17	9.260	1.083	4.476	1.00	99.99
ATOM	147	N	LEU	18	10.526	1.346	7.130	0.00	0.00
ATOM	148	CA	LEU	18	10.896	2.050	8.354	0.00	0.00
ATOM	149	C	LEU	18	9.673	2.268	9.259	0.00	0.00
ATOM	150	O	LEU	18	9.849	2.384	10.469	0.00	0.00
ATOM	151	CB	LEU	18	11.530	3.403	7.987	0.00	0.00
ATOM	152	CG	LEU	18	12.879	3.286	7.245	0.00	0.00
ATOM	153	CD1	LEU	18	13.301	4.670	6.731	0.00	0.00
ATOM	154	CD2	LEU	18	13.990	2.715	8.140	0.00	0.00
ATOM	155	H	LEU	18	10.403	1.897	6.291	1.00	99.99
ATOM	156	N	LEU	19	8.455	2.272	8.688	0.00	0.00
ATOM	157	CA	LEU	19	7.175	2.286	9.391	0.00	0.00
ATOM	158	C	LEU	19	7.100	1.105	10.352	0.00	0.00
ATOM	159	O	LEU	19	7.062	1.310	11.560	0.00	0.00
ATOM	160	CB	LEU	19	6.037	2.266	8.350	0.00	0.00
ATOM	161	CG	LEU	19	4.564	2.181	8.822	0.00	0.00
ATOM	162	CD1	LEU	19	3.673	2.526	7.617	0.00	0.00
ATOM	163	CD2	LEU	19	4.122	0.794	9.310	0.00	0.00
ATOM	164	H	LEU	19	8.412	2.195	7.682	1.00	99.99
ATOM	165	N	VAL	20	7.099	-0.124	9.817	0.00	0.00
ATOM	166	CA	VAL	20	7.026	-1.355	10.600	0.00	0.00
ATOM	167	C	VAL	20	8.206	-1.469	11.574	0.00	0.00
ATOM	168	O	VAL	20	8.066	-2.124	12.595	0.00	0.00
ATOM	169	CB	VAL	20	6.989	-2.580	9.653	0.00	0.00
ATOM	170	CG1	VAL	20	8.119	-2.645	8.621	0.00	0.00
ATOM	171	CG2	VAL	20	6.980	-3.921	10.402	0.00	0.00
ATOM	172	H	VAL	20	7.136	-0.212	8.812	1.00	99.99
ATOM	173	N	ILE	21	9.352	-0.836	11.298	0.00	0.00
ATOM	174	CA	ILE	21	10.528	-0.887	12.162	0.00	0.00
ATOM	175	C	ILE	21	10.424	0.026	13.399	0.00	0.00
ATOM	176	O	ILE	21	11.224	-0.096	14.325	0.00	0.00
ATOM	177	CB	ILE	21	11.791	-0.637	11.286	0.00	0.00
ATOM	178	CG1	ILE	21	12.131	-1.951	10.542	0.00	0.00
ATOM	179	CG2	ILE	21	13.035	-0.126	12.041	0.00	0.00
ATOM	180	CD1	ILE	21	13.210	-1.823	9.459	0.00	0.00
ATOM	181	H	ILE	21	9.423	-0.304	10.442	1.00	99.99
ATOM	182	N	THR	22	9.416	0.897	13.457	0.00	0.00
ATOM	183	CA	THR	22	9.194	1.847	14.547	0.00	0.00
ATOM	184	C	THR	22	7.815	1.661	15.193	0.00	0.00
ATOM	185	O	THR	22	7.609	2.107	16.321	0.00	0.00

ATOM	186	CB	THR	22	9.414	3.264	14.009	0.00	0.00
ATOM	187	OG1	THR	22	8.581	3.498	12.893	0.00	0.00
ATOM	188	CG2	THR	22	10.872	3.533	13.616	0.00	0.00
ATOM	189	H	THR	22	8.797	0.973	12.660	1.00	99.99
ATOM	190	HG1	THR	22	8.828	4.336	12.498	1.00	99.99
ATOM	191	N	GLU	23	6.921	0.913	14.532	0.00	0.00
ATOM	192	CA	GLU	23	5.869	0.133	15.163	0.00	0.00
ATOM	193	C	GLU	23	6.524	-1.009	15.951	0.00	0.00
ATOM	194	O	GLU	23	6.407	-1.064	17.174	0.00	0.00
ATOM	195	CB	GLU	23	4.942	-0.441	14.072	0.00	0.00
ATOM	196	CG	GLU	23	4.169	0.583	13.237	0.00	0.00
ATOM	197	CD	GLU	23	3.536	1.675	14.085	0.00	0.00
ATOM	198	OE1	GLU	23	3.811	2.853	13.765	0.00	0.00
ATOM	199	OE2	GLU	23	2.807	1.311	15.035	0.00	0.00
ATOM	200	H	GLU	23	7.134	0.672	13.574	1.00	99.99
ATOM	201	N	THR	24	7.207	-1.911	15.230	0.00	0.00
ATOM	202	CA	THR	24	7.853	-3.115	15.730	0.00	0.00
ATOM	203	C	THR	24	9.332	-2.850	16.043	0.00	0.00
ATOM	204	O	THR	24	9.669	-2.599	17.199	0.00	0.00
ATOM	205	CB	THR	24	7.648	-4.324	14.798	0.00	0.00
ATOM	206	OG1	THR	24	6.269	-4.511	14.554	0.00	0.00
ATOM	207	CG2	THR	24	8.232	-5.603	15.416	0.00	0.00
ATOM	208	H	THR	24	7.247	-1.772	14.230	1.00	99.99
ATOM	209	HG1	THR	24	6.167	-5.285	13.990	1.00	99.99
HETATM	210	N	NME	25	10.210	-2.958	15.034	0.00	0.00
HETATM	211	H	NME	25	9.852	-3.136	14.107	0.00	0.00
HETATM	212	CA	NME	25	11.655	-2.967	15.204	0.00	0.00
ATOM	213	N	GLU	27	-0.535	9.247	-17.473	0.00	0.00
ATOM	214	CA	GLU	27	0.219	8.675	-16.354	0.00	0.00
ATOM	215	C	GLU	27	0.813	9.739	-15.411	0.00	0.00
ATOM	216	O	GLU	27	1.147	9.425	-14.273	0.00	0.00
ATOM	217	CB	GLU	27	1.299	7.732	-16.918	0.00	0.00
ATOM	218	CG	GLU	27	2.095	6.942	-15.861	0.00	0.00
ATOM	219	CD	GLU	27	1.211	6.217	-14.838	0.00	0.00
ATOM	220	OE1	GLU	27	1.511	6.346	-13.630	0.00	0.00
ATOM	221	OE2	GLU	27	0.245	5.554	-15.275	0.00	0.00
ATOM	222	H	GLU	27	-0.238	8.982	-18.401	1.00	99.99
ATOM	223	N	LYS	28	0.913	11.001	-15.851	0.00	0.00
ATOM	224	CA	LYS	28	1.469	12.100	-15.071	0.00	0.00
ATOM	225	C	LYS	28	0.543	12.544	-13.934	0.00	0.00
ATOM	226	O	LYS	28	1.027	12.826	-12.838	0.00	0.00
ATOM	227	CB	LYS	28	1.786	13.290	-15.996	0.00	0.00
ATOM	228	CG	LYS	28	3.109	13.161	-16.775	0.00	0.00
ATOM	229	CD	LYS	28	3.135	12.037	-17.826	0.00	0.00
ATOM	230	CE	LYS	28	4.426	12.051	-18.653	0.00	0.00
ATOM	231	NZ	LYS	28	4.509	13.225	-19.543	0.00	0.00
ATOM	232	H	LYS	28	0.598	11.204	-16.789	1.00	99.99
ATOM	233	HZ1	LYS	28	4.489	14.071	-18.991	1.00	99.99
ATOM	234	HZ2	LYS	28	5.370	13.192	-20.071	1.00	99.99
ATOM	235	HZ3	LYS	28	3.726	13.225	-20.181	1.00	99.99
ATOM	236	N	MET	29	-0.774	12.590	-14.176	0.00	0.00
ATOM	237	CA	MET	29	-1.764	12.813	-13.125	0.00	0.00
ATOM	238	C	MET	29	-1.955	11.542	-12.291	0.00	0.00
ATOM	239	O	MET	29	-2.253	11.652	-11.107	0.00	0.00
ATOM	240	CB	MET	29	-3.085	13.267	-13.769	0.00	0.00
ATOM	241	CG	MET	29	-4.161	13.651	-12.744	0.00	0.00
ATOM	242	SD	MET	29	-3.692	14.972	-11.590	0.00	0.00
ATOM	243	CE	MET	29	-5.246	15.139	-10.676	0.00	0.00
ATOM	244	H	MET	29	-1.112	12.342	-15.095	1.00	99.99
ATOM	245	N	THR	30	-1.747	10.351	-12.877	0.00	0.00
ATOM	246	CA	THR	30	-1.852	9.072	-12.179	0.00	0.00
ATOM	247	C	THR	30	-0.788	8.952	-11.081	0.00	0.00
ATOM	248	O	THR	30	-1.121	8.605	-9.948	0.00	0.00
ATOM	249	CB	THR	30	-1.754	7.896	-13.169	0.00	0.00
ATOM	250	OG1	THR	30	-2.715	8.038	-14.195	0.00	0.00

ATOM	251	CG2	THR	30	-1.994	6.541	-12.493	0.00	0.00
ATOM	252	H	THR	30	-1.520	10.320	-13.862	1.00	99.99
ATOM	253	HG1	THR	30	-2.650	7.272	-14.770	1.00	99.99
ATOM	254	N	LEU	31	0.480	9.258	-11.400	0.00	0.00
ATOM	255	CA	LEU	31	1.562	9.251	-10.421	0.00	0.00
ATOM	256	C	LEU	31	1.454	10.399	-9.416	0.00	0.00
ATOM	257	O	LEU	31	1.930	10.247	-8.295	0.00	0.00
ATOM	258	CB	LEU	31	2.937	9.148	-11.113	0.00	0.00
ATOM	259	CG	LEU	31	3.392	10.353	-11.965	0.00	0.00
ATOM	260	CD1	LEU	31	4.096	11.445	-11.142	0.00	0.00
ATOM	261	CD2	LEU	31	4.365	9.882	-13.057	0.00	0.00
ATOM	262	H	LEU	31	0.706	9.505	-12.355	1.00	99.99
ATOM	263	N	CYS	32	0.786	11.507	-9.773	0.00	0.00
ATOM	264	CA	CYS	32	0.488	12.593	-8.848	0.00	0.00
ATOM	265	C	CYS	32	-0.529	12.134	-7.800	0.00	0.00
ATOM	266	O	CYS	32	-0.267	12.312	-6.612	0.00	0.00
ATOM	267	CB	CYS	32	-0.021	13.806	-9.638	0.00	0.00
ATOM	268	SG	CYS	32	-0.259	15.217	-8.524	0.00	0.00
ATOM	269	H	CYS	32	0.420	11.576	-10.712	1.00	99.99
ATOM	270	HG	CYS	32	-0.695	16.067	-9.459	1.00	99.99
ATOM	271	N	ILE	33	-1.659	11.529	-8.216	0.00	0.00
ATOM	272	CA	ILE	33	-2.684	11.082	-7.275	0.00	0.00
ATOM	273	C	ILE	33	-2.165	9.989	-6.339	0.00	0.00
ATOM	274	O	ILE	33	-2.443	10.052	-5.146	0.00	0.00
ATOM	275	CB	ILE	33	-4.048	10.729	-7.917	0.00	0.00
ATOM	276	CG1	ILE	33	-3.996	9.546	-8.906	0.00	0.00
ATOM	277	CG2	ILE	33	-4.660	11.993	-8.547	0.00	0.00
ATOM	278	CD1	ILE	33	-5.371	9.049	-9.368	0.00	0.00
ATOM	279	H	ILE	33	-1.826	11.401	-9.205	1.00	99.99
ATOM	280	N	SER	34	-1.357	9.045	-6.837	0.00	0.00
ATOM	281	CA	SER	34	-0.735	8.012	-6.015	0.00	0.00
ATOM	282	C	SER	34	0.223	8.612	-4.976	0.00	0.00
ATOM	283	O	SER	34	0.245	8.145	-3.839	0.00	0.00
ATOM	284	CB	SER	34	0.006	7.043	-6.945	0.00	0.00
ATOM	285	OG	SER	34	0.534	5.957	-6.216	0.00	0.00
ATOM	286	H	SER	34	-1.155	9.048	-7.828	1.00	99.99
ATOM	287	HG	SER	34	0.980	5.365	-6.827	1.00	99.99
ATOM	288	N	VAL	35	0.977	9.659	-5.348	0.00	0.00
ATOM	289	CA	VAL	35	1.896	10.368	-4.458	0.00	0.00
ATOM	290	C	VAL	35	1.161	11.169	-3.369	0.00	0.00
ATOM	291	O	VAL	35	1.709	11.328	-2.279	0.00	0.00
ATOM	292	CB	VAL	35	2.886	11.226	-5.285	0.00	0.00
ATOM	293	CG1	VAL	35	3.608	12.321	-4.481	0.00	0.00
ATOM	294	CG2	VAL	35	3.967	10.314	-5.894	0.00	0.00
ATOM	295	H	VAL	35	0.909	9.995	-6.300	1.00	99.99
ATOM	296	N	LEU	36	-0.080	11.622	-3.604	0.00	0.00
ATOM	297	CA	LEU	36	-0.880	12.257	-2.558	0.00	0.00
ATOM	298	C	LEU	36	-1.235	11.257	-1.456	0.00	0.00
ATOM	299	O	LEU	36	-1.056	11.566	-0.279	0.00	0.00
ATOM	300	CB	LEU	36	-2.151	12.903	-3.141	0.00	0.00
ATOM	301	CG	LEU	36	-1.895	14.123	-4.052	0.00	0.00
ATOM	302	CD1	LEU	36	-3.205	14.536	-4.738	0.00	0.00
ATOM	303	CD2	LEU	36	-1.332	15.324	-3.278	0.00	0.00
ATOM	304	H	LEU	36	-0.499	11.480	-4.513	1.00	99.99
ATOM	305	N	LEU	37	-1.689	10.055	-1.837	0.00	0.00
ATOM	306	CA	LEU	37	-1.984	8.972	-0.906	0.00	0.00
ATOM	307	C	LEU	37	-0.716	8.338	-0.311	0.00	0.00
ATOM	308	O	LEU	37	-0.817	7.630	0.692	0.00	0.00
ATOM	309	CB	LEU	37	-2.887	7.925	-1.582	0.00	0.00
ATOM	310	CG	LEU	37	-4.345	8.358	-1.869	0.00	0.00
ATOM	311	CD1	LEU	37	-5.010	9.090	-0.690	0.00	0.00
ATOM	312	CD2	LEU	37	-4.546	9.184	-3.141	0.00	0.00
ATOM	313	H	LEU	37	-1.806	9.870	-2.825	1.00	99.99
ATOM	314	N	ALA	38	0.471	8.626	-0.867	0.00	0.00
ATOM	315	CA	ALA	38	1.740	8.226	-0.280	0.00	0.00

ATOM	316	C	ALA	38	2.066	9.043	0.973	0.00	0.00
ATOM	317	O	ALA	38	2.474	8.464	1.980	0.00	0.00
ATOM	318	CB	ALA	38	2.864	8.324	-1.312	0.00	0.00
ATOM	319	H	ALA	38	0.497	9.193	-1.702	1.00	99.99
ATOM	320	N	LEU	39	1.855	10.367	0.926	0.00	0.00
ATOM	321	CA	LEU	39	2.012	11.251	2.080	0.00	0.00
ATOM	322	C	LEU	39	0.881	11.068	3.102	0.00	0.00
ATOM	323	O	LEU	39	1.101	11.338	4.283	0.00	0.00
ATOM	324	CB	LEU	39	2.100	12.720	1.618	0.00	0.00
ATOM	325	CG	LEU	39	3.511	13.226	1.241	0.00	0.00
ATOM	326	CD1	LEU	39	4.467	13.237	2.446	0.00	0.00
ATOM	327	CD2	LEU	39	4.151	12.457	0.077	0.00	0.00
ATOM	328	H	LEU	39	1.526	10.778	0.063	1.00	99.99
ATOM	329	N	THR	40	-0.291	10.561	2.686	0.00	0.00
ATOM	330	CA	THR	40	-1.360	10.158	3.602	0.00	0.00
ATOM	331	C	THR	40	-0.873	9.037	4.530	0.00	0.00
ATOM	332	O	THR	40	-1.089	9.092	5.741	0.00	0.00
ATOM	333	CB	THR	40	-2.627	9.753	2.826	0.00	0.00
ATOM	334	OG1	THR	40	-3.079	10.847	2.055	0.00	0.00
ATOM	335	CG2	THR	40	-3.778	9.334	3.747	0.00	0.00
ATOM	336	H	THR	40	-0.432	10.397	1.699	1.00	99.99
ATOM	337	HG1	THR	40	-3.887	10.588	1.606	1.00	99.99
ATOM	338	N	VAL	41	-0.182	8.048	3.954	0.00	0.00
ATOM	339	CA	VAL	41	0.382	6.891	4.637	0.00	0.00
ATOM	340	C	VAL	41	1.737	7.181	5.315	0.00	0.00
ATOM	341	O	VAL	41	2.285	6.307	5.986	0.00	0.00
ATOM	342	CB	VAL	41	0.606	5.759	3.640	0.00	99.99
ATOM	343	CG1	VAL	41	1.502	4.697	4.271	0.00	99.99
ATOM	344	CG2	VAL	41	-0.733	5.135	3.266	0.00	99.99
ATOM	345	N	PHE	42	2.270	8.402	5.164	0.00	0.00
ATOM	346	CA	PHE	42	3.482	8.875	5.827	0.00	0.00
ATOM	347	C	PHE	42	3.150	9.624	7.120	0.00	0.00
ATOM	348	O	PHE	42	3.879	9.495	8.097	0.00	0.00
ATOM	349	CB	PHE	42	4.246	9.781	4.851	0.00	0.00
ATOM	350	CG	PHE	42	5.642	10.167	5.296	0.00	0.00
ATOM	351	CD1	PHE	42	5.921	11.481	5.719	0.00	0.00
ATOM	352	CD2	PHE	42	6.676	9.213	5.258	0.00	0.00
ATOM	353	CE1	PHE	42	7.227	11.835	6.101	0.00	0.00
ATOM	354	CE2	PHE	42	7.980	9.564	5.650	0.00	0.00
ATOM	355	CZ	PHE	42	8.255	10.876	6.071	0.00	0.00
ATOM	356	H	PHE	42	1.783	9.065	4.577	1.00	99.99
ATOM	357	N	LEU	43	2.031	10.360	7.154	0.00	0.00
ATOM	358	CA	LEU	43	1.473	10.924	8.382	0.00	0.00
ATOM	359	C	LEU	43	0.874	9.828	9.281	0.00	0.00
ATOM	360	O	LEU	43	0.769	10.036	10.491	0.00	0.00
ATOM	361	CB	LEU	43	0.398	11.963	8.019	0.00	0.00
ATOM	362	CG	LEU	43	0.943	13.203	7.276	0.00	0.00
ATOM	363	CD1	LEU	43	-0.231	14.055	6.775	0.00	0.00
ATOM	364	CD2	LEU	43	1.853	14.063	8.168	0.00	0.00
ATOM	365	H	LEU	43	1.484	10.457	6.309	1.00	99.99
ATOM	366	N	LEU	44	0.536	8.658	8.710	0.00	0.00
ATOM	367	CA	LEU	44	0.132	7.461	9.440	0.00	0.00
ATOM	368	C	LEU	44	1.236	7.030	10.392	0.00	0.00
ATOM	369	O	LEU	44	1.015	7.010	11.603	0.00	0.00
ATOM	370	CB	LEU	44	-0.237	6.330	8.461	0.00	0.00
ATOM	371	CG	LEU	44	-0.598	4.940	9.053	0.00	0.00
ATOM	372	CD1	LEU	44	-1.120	4.095	7.887	0.00	0.00
ATOM	373	CD2	LEU	44	0.548	4.126	9.682	0.00	0.00
ATOM	374	H	LEU	44	0.627	8.573	7.707	1.00	99.99
ATOM	375	N	LEU	45	2.406	6.671	9.845	0.00	0.00
ATOM	376	CA	LEU	45	3.519	6.170	10.638	0.00	0.00
ATOM	377	C	LEU	45	4.079	7.261	11.561	0.00	0.00
ATOM	378	O	LEU	45	4.821	6.946	12.478	0.00	0.00
ATOM	379	CB	LEU	45	4.613	5.598	9.712	0.00	0.00
ATOM	380	CG	LEU	45	5.541	6.618	9.012	0.00	0.00

ATOM	381	CD1	LEU	45	6.887	6.784	9.737	0.00	0.00
ATOM	382	CD2	LEU	45	5.832	6.220	7.559	0.00	0.00
ATOM	383	H	LEU	45	2.516	6.707	8.841	1.00	99.99
ATOM	384	N	ILE	46	3.724	8.534	11.345	0.00	0.00
ATOM	385	CA	ILE	46	4.148	9.666	12.160	0.00	0.00
ATOM	386	C	ILE	46	3.185	9.956	13.327	0.00	0.00
ATOM	387	O	ILE	46	3.473	10.794	14.180	0.00	0.00
ATOM	388	CB	ILE	46	4.432	10.867	11.210	0.00	0.00
ATOM	389	CG1	ILE	46	5.801	10.618	10.528	0.00	0.00
ATOM	390	CG2	ILE	46	4.416	12.260	11.869	0.00	0.00
ATOM	391	CD1	ILE	46	6.159	11.602	9.409	0.00	0.00
ATOM	392	H	ILE	46	3.121	8.734	10.560	1.00	99.99
ATOM	393	N	SER	47	2.082	9.209	13.426	0.00	0.00
ATOM	394	CA	SER	47	1.150	9.252	14.548	0.00	0.00
ATOM	395	C	SER	47	0.919	7.870	15.169	0.00	0.00
ATOM	396	O	SER	47	0.237	7.783	16.189	0.00	0.00
ATOM	397	CB	SER	47	-0.126	9.962	14.095	0.00	0.00
ATOM	398	OG	SER	47	-0.740	9.307	13.001	0.00	0.00
ATOM	399	H	SER	47	1.886	8.542	12.690	1.00	99.99
ATOM	400	HG	SER	47	-0.178	9.413	12.226	1.00	99.99
ATOM	401	N	LYS	48	1.561	6.825	14.617	0.00	0.00
ATOM	402	CA	LYS	48	1.788	5.536	15.262	0.00	0.00
ATOM	403	C	LYS	48	3.272	5.283	15.588	0.00	0.00
ATOM	404	O	LYS	48	3.543	4.430	16.432	0.00	0.00
ATOM	405	CB	LYS	48	1.158	4.403	14.455	0.00	0.00
ATOM	406	CG	LYS	48	-0.354	4.284	14.642	0.00	0.00
ATOM	407	CD	LYS	48	-0.773	3.894	16.077	0.00	0.00
ATOM	408	CE	LYS	48	-1.189	5.103	16.921	0.00	0.00
ATOM	409	NZ	LYS	48	-1.702	4.693	18.239	0.00	0.00
ATOM	410	H	LYS	48	2.046	6.979	13.746	1.00	99.99
ATOM	411	HZ1	LYS	48	-1.012	4.132	18.717	1.00	99.99
ATOM	412	HZ2	LYS	48	-1.914	5.513	18.789	1.00	99.99
ATOM	413	HZ3	LYS	48	-2.552	4.158	18.112	1.00	99.99
ATOM	414	N	ILE	49	4.204	6.096	15.057	0.00	0.00
ATOM	415	CA	ILE	49	5.427	6.457	15.769	0.00	0.00
ATOM	416	C	ILE	49	5.527	7.970	16.024	0.00	0.00
ATOM	417	O	ILE	49	5.311	8.399	17.157	0.00	0.00
ATOM	418	CB	ILE	49	6.732	5.740	15.337	0.00	0.00
ATOM	419	CG1	ILE	49	7.793	5.862	16.468	0.00	0.00
ATOM	420	CG2	ILE	49	7.308	6.108	13.955	0.00	0.00
ATOM	421	CD1	ILE	49	8.665	7.127	16.501	0.00	0.00
ATOM	422	H	ILE	49	3.931	6.719	14.311	1.00	99.99
HETATM	423	N	NME	50	5.876	8.773	15.013	0.00	0.00
HETATM	424	H	NME	50	5.998	8.361	14.099	0.00	0.00
HETATM	425	CA	NME	50	6.271	10.165	15.177	0.00	0.00
ATOM	426	N	GLU	52	-8.968	2.364	-17.452	0.00	0.00
ATOM	427	CA	GLU	52	-8.186	2.902	-16.335	0.00	0.00
ATOM	428	C	GLU	52	-9.010	3.796	-15.388	0.00	0.00
ATOM	429	O	GLU	52	-8.603	4.015	-14.251	0.00	0.00
ATOM	430	CB	GLU	52	-6.955	3.634	-16.901	0.00	0.00
ATOM	431	CG	GLU	52	-5.951	4.138	-15.847	0.00	0.00
ATOM	432	CD	GLU	52	-5.535	3.066	-14.831	0.00	0.00
ATOM	433	OE1	GLU	52	-5.559	3.384	-13.621	0.00	0.00
ATOM	434	OE2	GLU	52	-5.211	1.942	-15.275	0.00	0.00
ATOM	435	H	GLU	52	-8.628	2.567	-18.381	1.00	99.99
ATOM	436	N	LYS	53	-10.180	4.283	-15.824	0.00	0.00
ATOM	437	CA	LYS	53	-11.053	5.150	-15.040	0.00	0.00
ATOM	438	C	LYS	53	-11.761	4.405	-13.903	0.00	0.00
ATOM	439	O	LYS	53	-11.891	4.952	-12.809	0.00	0.00
ATOM	440	CB	LYS	53	-12.089	5.818	-15.963	0.00	0.00
ATOM	441	CG	LYS	53	-11.559	7.029	-16.754	0.00	0.00
ATOM	442	CD	LYS	53	-10.494	6.696	-17.814	0.00	0.00
ATOM	443	CE	LYS	53	-10.117	7.919	-18.658	0.00	0.00
ATOM	444	NZ	LYS	53	-11.217	8.353	-19.541	0.00	0.00
ATOM	445	H	LYS	53	-10.473	4.046	-16.760	1.00	99.99

ATOM	446	HZ1	LYS	53	-12.022	8.601	-18.983	1.00	99.99
ATOM	447	HZ2	LYS	53	-10.924	9.156	-20.080	1.00	99.99
ATOM	448	HZ3	LYS	53	-11.465	7.602	-20.169	1.00	99.99
ATOM	449	N	VAL	54	-12.200	3.164	-14.148	0.00	0.00
ATOM	450	CA	VAL	54	-12.728	2.277	-13.112	0.00	0.00
ATOM	451	C	VAL	54	-11.569	1.741	-12.265	0.00	0.00
ATOM	452	O	VAL	54	-11.753	1.551	-11.068	0.00	0.00
ATOM	453	CB	VAL	54	-13.527	1.124	-13.765	0.00	0.00
ATOM	454	CG1	VAL	54	-14.079	0.140	-12.718	0.00	0.00
ATOM	455	CG2	VAL	54	-14.713	1.664	-14.584	0.00	0.00
ATOM	456	H	VAL	54	-12.057	2.773	-15.068	1.00	99.99
ATOM	457	N	THR	55	-10.381	1.536	-12.859	0.00	0.00
ATOM	458	CA	THR	55	-9.194	1.046	-12.162	0.00	0.00
ATOM	459	C	THR	55	-8.748	2.021	-11.065	0.00	0.00
ATOM	460	O	THR	55	-8.516	1.595	-9.933	0.00	0.00
ATOM	461	CB	THR	55	-8.048	0.775	-13.155	0.00	0.00
ATOM	462	OG1	THR	55	-8.483	-0.094	-14.180	0.00	0.00
ATOM	463	CG2	THR	55	-6.833	0.127	-12.482	0.00	0.00
ATOM	464	H	THR	55	-10.295	1.697	-13.853	1.00	99.99
ATOM	465	HG1	THR	55	-7.736	-0.269	-14.758	1.00	99.99
ATOM	466	N	LEU	56	-8.652	3.321	-11.382	0.00	0.00
ATOM	467	CA	LEU	56	-8.307	4.347	-10.403	0.00	0.00
ATOM	468	C	LEU	56	-9.428	4.598	-9.393	0.00	0.00
ATOM	469	O	LEU	56	-9.129	5.005	-8.274	0.00	0.00
ATOM	470	CB	LEU	56	-7.786	5.623	-11.095	0.00	0.00
ATOM	471	CG	LEU	56	-8.796	6.430	-11.941	0.00	0.00
ATOM	472	CD1	LEU	56	-9.612	7.436	-11.112	0.00	0.00
ATOM	473	CD2	LEU	56	-8.052	7.211	-13.035	0.00	0.00
ATOM	474	H	LEU	56	-8.821	3.613	-12.336	1.00	99.99
ATOM	475	N	CYS	57	-10.690	4.306	-9.743	0.00	0.00
ATOM	476	CA	CYS	57	-11.808	4.362	-8.810	0.00	0.00
ATOM	477	C	CYS	57	-11.684	3.250	-7.764	0.00	0.00
ATOM	478	O	CYS	57	-11.771	3.550	-6.575	0.00	0.00
ATOM	479	CB	CYS	57	-13.128	4.274	-9.585	0.00	0.00
ATOM	480	SG	CYS	57	-14.524	4.525	-8.455	0.00	0.00
ATOM	481	H	CYS	57	-10.875	3.975	-10.679	1.00	99.99
ATOM	482	HG	CYS	57	-15.482	4.408	-9.379	1.00	99.99
ATOM	483	N	ILE	58	-11.457	1.991	-8.183	0.00	0.00
ATOM	484	CA	ILE	58	-11.358	0.867	-7.251	0.00	0.00
ATOM	485	C	ILE	58	-10.147	0.986	-6.321	0.00	0.00
ATOM	486	O	ILE	58	-10.272	0.671	-5.140	0.00	0.00
ATOM	487	CB	ILE	58	-11.468	-0.528	-7.914	0.00	0.00
ATOM	488	CG1	ILE	58	-10.334	-0.841	-8.910	0.00	0.00
ATOM	489	CG2	ILE	58	-12.863	-0.690	-8.546	0.00	0.00
ATOM	490	CD1	ILE	58	-10.300	-2.298	-9.389	0.00	0.00
ATOM	491	H	ILE	58	-11.384	1.798	-9.172	1.00	99.99
ATOM	492	N	SER	59	-9.013	1.503	-6.811	0.00	0.00
ATOM	493	CA	SER	59	-7.835	1.772	-5.994	0.00	0.00
ATOM	494	C	SER	59	-8.108	2.867	-4.953	0.00	0.00
ATOM	495	O	SER	59	-7.648	2.750	-3.818	0.00	0.00
ATOM	496	CB	SER	59	-6.690	2.182	-6.928	0.00	0.00
ATOM	497	OG	SER	59	-5.491	2.352	-6.204	0.00	0.00
ATOM	498	H	SER	59	-8.973	1.742	-7.793	1.00	99.99
ATOM	499	HG	SER	59	-4.792	2.591	-6.818	1.00	99.99
ATOM	500	N	VAL	60	-8.876	3.905	-5.322	0.00	0.00
ATOM	501	CA	VAL	60	-9.265	4.998	-4.432	0.00	0.00
ATOM	502	C	VAL	60	-10.280	4.554	-3.361	0.00	0.00
ATOM	503	O	VAL	60	-10.318	5.159	-2.290	0.00	0.00
ATOM	504	CB	VAL	60	-9.741	6.215	-5.265	0.00	0.00
ATOM	505	CG1	VAL	60	-10.541	7.263	-4.472	0.00	0.00
ATOM	506	CG2	VAL	60	-8.517	6.933	-5.864	0.00	0.00
ATOM	507	H	VAL	60	-9.223	3.940	-6.272	1.00	99.99
ATOM	508	N	LEU	61	-11.052	3.480	-3.581	0.00	0.00
ATOM	509	CA	LEU	61	-11.901	2.915	-2.534	0.00	0.00
ATOM	510	C	LEU	61	-11.060	2.250	-1.440	0.00	0.00

ATOM	511	O	LEU	61	-11.309	2.485	-0.258	0.00	0.00
ATOM	512	CB	LEU	61	-12.909	1.910	-3.123	0.00	0.00
ATOM	513	CG	LEU	61	-13.994	2.537	-4.025	0.00	0.00
ATOM	514	CD1	LEU	61	-14.799	1.424	-4.710	0.00	0.00
ATOM	515	CD2	LEU	61	-14.957	3.442	-3.241	0.00	0.00
ATOM	516	H	LEU	61	-11.008	3.009	-4.474	1.00	99.99
ATOM	517	N	LEU	62	-10.049	1.457	-1.829	0.00	0.00
ATOM	518	CA	LEU	62	-9.102	0.850	-0.897	0.00	0.00
ATOM	519	C	LEU	62	-8.155	1.886	-0.271	0.00	0.00
ATOM	520	O	LEU	62	-7.590	1.612	0.785	0.00	0.00
ATOM	521	CB	LEU	62	-8.300	-0.270	-1.593	0.00	0.00
ATOM	522	CG	LEU	62	-9.018	-1.623	-1.814	0.00	0.00
ATOM	523	CD1	LEU	62	-9.643	-2.189	-0.530	0.00	0.00
ATOM	524	CD2	LEU	62	-10.062	-1.618	-2.934	0.00	0.00
ATOM	525	H	LEU	62	-9.900	1.302	-2.817	1.00	99.99
ATOM	526	N	SER	63	-8.017	3.082	-0.864	0.00	0.00
ATOM	527	CA	SER	63	-7.286	4.186	-0.257	0.00	0.00
ATOM	528	C	SER	63	-7.974	4.660	1.024	0.00	0.00
ATOM	529	O	SER	63	-7.322	4.753	2.063	0.00	0.00
ATOM	530	CB	SER	63	-7.134	5.342	-1.243	0.00	0.00
ATOM	531	OG	SER	63	-6.568	6.434	-0.563	0.00	0.00
ATOM	532	H	SER	63	-8.482	3.248	-1.746	1.00	99.99
ATOM	533	HG	SER	63	-6.465	7.161	-1.181	1.00	99.99
ATOM	534	N	LEU	64	-9.281	4.947	0.953	0.00	0.00
ATOM	535	CA	LEU	64	-10.062	5.363	2.111	0.00	0.00
ATOM	536	C	LEU	64	-10.212	4.225	3.132	0.00	0.00
ATOM	537	O	LEU	64	-10.375	4.517	4.317	0.00	0.00
ATOM	538	CB	LEU	64	-11.442	5.887	1.664	0.00	0.00
ATOM	539	CG	LEU	64	-11.507	7.384	1.285	0.00	0.00
ATOM	540	CD1	LEU	64	-11.224	8.300	2.487	0.00	0.00
ATOM	541	CD2	LEU	64	-10.589	7.768	0.116	0.00	0.00
ATOM	542	H	LEU	64	-9.759	4.859	0.066	1.00	99.99
ATOM	543	N	THR	65	-10.100	2.951	2.714	0.00	0.00
ATOM	544	CA	THR	65	-10.084	1.818	3.641	0.00	0.00
ATOM	545	C	THR	65	-8.814	1.779	4.506	0.00	0.00
ATOM	546	O	THR	65	-8.851	1.294	5.636	0.00	0.00
ATOM	547	CB	THR	65	-10.415	0.492	2.913	0.00	0.00
ATOM	548	OG1	THR	65	-11.537	-0.097	3.538	0.00	0.00
ATOM	549	CG2	THR	65	-9.313	-0.575	2.884	0.00	0.00
ATOM	550	H	THR	65	-9.981	2.765	1.727	1.00	99.99
ATOM	551	HG1	THR	65	-11.768	-0.893	3.055	1.00	99.99
ATOM	552	N	VAL	66	-7.719	2.353	3.997	0.00	0.00
ATOM	553	CA	VAL	66	-6.420	2.502	4.649	0.00	0.00
ATOM	554	C	VAL	66	-6.284	3.892	5.313	0.00	0.00
ATOM	555	O	VAL	66	-5.310	4.144	6.024	0.00	0.00
ATOM	556	CB	VAL	66	-5.352	2.198	3.567	0.00	0.00
ATOM	557	CG1	VAL	66	-3.925	2.559	3.978	0.00	0.00
ATOM	558	CG2	VAL	66	-5.379	0.698	3.225	0.00	0.00
ATOM	559	H	VAL	66	-7.786	2.732	3.062	1.00	99.99
ATOM	560	N	PHE	67	-7.276	4.781	5.148	0.00	0.00
ATOM	561	CA	PHE	67	-7.349	6.061	5.845	0.00	0.00
ATOM	562	C	PHE	67	-8.198	5.980	7.119	0.00	0.00
ATOM	563	O	PHE	67	-7.928	6.700	8.075	0.00	0.00
ATOM	564	CB	PHE	67	-7.920	7.118	4.892	0.00	0.00
ATOM	565	CG	PHE	67	-7.904	8.533	5.444	0.00	0.00
ATOM	566	CD1	PHE	67	-9.105	9.254	5.590	0.00	0.00
ATOM	567	CD2	PHE	67	-6.684	9.133	5.813	0.00	0.00
ATOM	568	CE1	PHE	67	-9.084	10.569	6.089	0.00	0.00
ATOM	569	CE2	PHE	67	-6.663	10.445	6.318	0.00	0.00
ATOM	570	CZ	PHE	67	-7.863	11.165	6.452	0.00	0.00
ATOM	571	H	PHE	67	-8.047	4.538	4.543	1.00	99.99
ATOM	572	N	LEU	68	-9.194	5.085	7.164	0.00	0.00
ATOM	573	CA	LEU	68	-9.898	4.738	8.397	0.00	0.00
ATOM	574	C	LEU	68	-9.014	3.871	9.307	0.00	0.00
ATOM	575	O	LEU	68	-9.191	3.913	10.521	0.00	0.00

ATOM	576	CB	LEU	68	-11.193	3.986	8.045	0.00	0.00
ATOM	577	CG	LEU	68	-12.237	4.842	7.296	0.00	0.00
ATOM	578	CD1	LEU	68	-13.375	3.941	6.799	0.00	0.00
ATOM	579	CD2	LEU	68	-12.818	5.958	8.179	0.00	0.00
ATOM	580	H	LEU	68	-9.408	4.549	6.335	1.00	99.99
ATOM	581	N	LEU	69	-8.046	3.136	8.730	0.00	0.00
ATOM	582	CA	LEU	69	-7.027	2.348	9.420	0.00	0.00
ATOM	583	C	LEU	69	-6.243	3.221	10.394	0.00	0.00
ATOM	584	O	LEU	69	-6.277	2.978	11.599	0.00	0.00
ATOM	585	CB	LEU	69	-6.105	1.703	8.363	0.00	0.00
ATOM	586	CG	LEU	69	-4.888	0.869	8.834	0.00	0.00
ATOM	587	CD1	LEU	69	-4.375	0.064	7.628	0.00	0.00
ATOM	588	CD2	LEU	69	-3.704	1.695	9.357	0.00	0.00
ATOM	589	H	LEU	69	-7.987	3.155	7.722	1.00	99.99
ATOM	590	N	VAL	70	-5.545	4.233	9.858	0.00	0.00
ATOM	591	CA	VAL	70	-4.762	5.203	10.615	0.00	0.00
ATOM	592	C	VAL	70	-5.649	5.978	11.595	0.00	0.00
ATOM	593	O	VAL	70	-5.145	6.438	12.606	0.00	0.00
ATOM	594	CB	VAL	70	-4.039	6.171	9.644	0.00	0.00
ATOM	595	CG1	VAL	70	-4.936	6.845	8.604	0.00	0.00
ATOM	596	CG2	VAL	70	-3.279	7.289	10.371	0.00	0.00
ATOM	597	H	VAL	70	-5.571	4.347	8.854	1.00	99.99
ATOM	598	N	ILE	71	-6.953	6.123	11.333	0.00	0.00
ATOM	599	CA	ILE	71	-7.867	6.881	12.184	0.00	0.00
ATOM	600	C	ILE	71	-8.368	6.088	13.406	0.00	0.00
ATOM	601	O	ILE	71	-8.968	6.678	14.304	0.00	0.00
ATOM	602	CB	ILE	71	-8.994	7.473	11.285	0.00	0.00
ATOM	603	CG1	ILE	71	-8.441	8.747	10.601	0.00	0.00
ATOM	604	CG2	ILE	71	-10.325	7.793	11.995	0.00	0.00
ATOM	605	CD1	ILE	71	-9.348	9.356	9.524	0.00	0.00
ATOM	606	H	ILE	71	-7.330	5.720	10.486	1.00	99.99
ATOM	607	N	THR	72	-8.079	4.786	13.497	0.00	0.00
ATOM	608	CA	THR	72	-8.423	3.957	14.657	0.00	0.00
ATOM	609	C	THR	72	-7.221	3.219	15.258	0.00	0.00
ATOM	610	O	THR	72	-7.312	2.686	16.361	0.00	0.00
ATOM	611	CB	THR	72	-9.641	3.075	14.346	0.00	0.00
ATOM	612	OG1	THR	72	-9.535	2.482	13.069	0.00	0.00
ATOM	613	CG2	THR	72	-10.949	3.875	14.377	0.00	0.00
ATOM	614	H	THR	72	-7.620	4.331	12.719	1.00	99.99
ATOM	615	HG1	THR	72	-10.353	2.020	12.878	1.00	99.99
ATOM	616	N	GLU	73	-6.070	3.306	14.587	0.00	0.00
ATOM	617	CA	GLU	73	-4.733	3.301	15.164	0.00	0.00
ATOM	618	C	GLU	73	-4.533	4.614	15.932	0.00	0.00
ATOM	619	O	GLU	73	-4.423	4.592	17.156	0.00	0.00
ATOM	620	CB	GLU	73	-3.762	3.156	13.982	0.00	0.00
ATOM	621	CG	GLU	73	-3.490	1.699	13.589	0.00	0.00
ATOM	622	CD	GLU	73	-2.451	1.055	14.506	0.00	0.00
ATOM	623	OE1	GLU	73	-2.795	0.776	15.677	0.00	0.00
ATOM	624	OE2	GLU	73	-1.312	0.867	14.029	0.00	0.00
ATOM	625	H	GLU	73	-6.119	3.677	13.648	1.00	99.99
ATOM	626	N	THR	74	-4.509	5.746	15.211	0.00	0.00
ATOM	627	CA	THR	74	-4.364	7.101	15.736	0.00	0.00
ATOM	628	C	THR	74	-5.716	7.672	16.183	0.00	0.00
ATOM	629	O	THR	74	-6.035	7.610	17.370	0.00	0.00
ATOM	630	CB	THR	74	-3.619	8.038	14.767	0.00	0.00
ATOM	631	OG1	THR	74	-2.398	7.442	14.386	0.00	0.00
ATOM	632	CG2	THR	74	-3.335	9.399	15.417	0.00	0.00
ATOM	633	H	THR	74	-4.599	5.666	14.208	1.00	99.99
ATOM	634	HG1	THR	74	-1.910	8.067	13.839	1.00	99.99
HETATM	635	N	NME	75	-6.476	8.270	15.254	0.00	0.00
HETATM	636	H	NME	75	-6.161	8.257	14.295	0.00	0.00
HETATM	637	CA	NME	75	-7.656	9.066	15.556	0.00	0.00
ATOM	638	N	GLU	77	-5.198	-7.652	-17.527	0.00	0.00
ATOM	639	CA	GLU	77	-5.391	-6.805	-16.347	0.00	0.00
ATOM	640	C	GLU	77	-6.465	-7.361	-15.396	0.00	0.00

ATOM	641	O	GLU	77	-6.549	-6.921	-14.253	0.00	0.00
ATOM	642	CB	GLU	77	-5.703	-5.373	-16.827	0.00	0.00
ATOM	643	CG	GLU	77	-5.866	-4.312	-15.722	0.00	0.00
ATOM	644	CD	GLU	77	-4.715	-4.292	-14.708	0.00	0.00
ATOM	645	OE1	GLU	77	-5.022	-4.256	-13.496	0.00	0.00
ATOM	646	OE2	GLU	77	-3.548	-4.318	-15.156	0.00	0.00
ATOM	647	H	GLU	77	-6.010	-7.846	-18.092	1.00	99.99
ATOM	648	N	LYS	78	-7.269	-8.342	-15.829	0.00	0.00
ATOM	649	CA	LYS	78	-8.386	-8.870	-15.048	0.00	0.00
ATOM	650	C	LYS	78	-7.926	-9.797	-13.917	0.00	0.00
ATOM	651	O	LYS	78	-8.500	-9.752	-12.830	0.00	0.00
ATOM	652	CB	LYS	78	-9.379	-9.594	-15.976	0.00	0.00
ATOM	653	CG	LYS	78	-10.375	-8.657	-16.686	0.00	0.00
ATOM	654	CD	LYS	78	-9.740	-7.666	-17.677	0.00	0.00
ATOM	655	CE	LYS	78	-10.794	-6.833	-18.416	0.00	0.00
ATOM	656	NZ	LYS	78	-11.598	-7.646	-19.349	0.00	0.00
ATOM	657	H	LYS	78	-7.144	-8.695	-16.766	1.00	99.99
ATOM	658	HZ1	LYS	78	-12.083	-8.370	-18.837	1.00	99.99
ATOM	659	HZ2	LYS	78	-12.275	-7.058	-19.816	1.00	99.99
ATOM	660	HZ3	LYS	78	-10.994	-8.071	-20.038	1.00	99.99
ATOM	661	N	MET	79	-6.883	-10.604	-14.152	0.00	0.00
ATOM	662	CA	MET	79	-6.210	-11.357	-13.097	0.00	0.00
ATOM	663	C	MET	79	-5.312	-10.435	-12.263	0.00	0.00
ATOM	664	O	MET	79	-5.123	-10.703	-11.082	0.00	0.00
ATOM	665	CB	MET	79	-5.404	-12.502	-13.733	0.00	0.00
ATOM	666	CG	MET	79	-4.757	-13.440	-12.706	0.00	0.00
ATOM	667	SD	MET	79	-5.911	-14.233	-11.550	0.00	0.00
ATOM	668	CE	MET	79	-4.751	-15.290	-10.646	0.00	0.00
ATOM	669	H	MET	79	-6.466	-10.607	-15.071	1.00	99.99
ATOM	670	N	THR	80	-4.794	-9.345	-12.850	0.00	0.00
ATOM	671	CA	THR	80	-3.932	-8.380	-12.171	0.00	0.00
ATOM	672	C	THR	80	-4.701	-7.631	-11.075	0.00	0.00
ATOM	673	O	THR	80	-4.208	-7.525	-9.951	0.00	0.00
ATOM	674	CB	THR	80	-3.313	-7.404	-13.188	0.00	0.00
ATOM	675	OG1	THR	80	-2.688	-8.125	-14.231	0.00	0.00
ATOM	676	CG2	THR	80	-2.263	-6.487	-12.550	0.00	0.00
ATOM	677	H	THR	80	-4.985	-9.175	-13.826	1.00	99.99
ATOM	678	HG1	THR	80	-2.352	-7.496	-14.876	1.00	99.99
ATOM	679	N	LEU	81	-5.914	-7.146	-11.381	0.00	0.00
ATOM	680	CA	LEU	81	-6.784	-6.508	-10.399	0.00	0.00
ATOM	681	C	LEU	81	-7.354	-7.502	-9.385	0.00	0.00
ATOM	682	O	LEU	81	-7.630	-7.100	-8.259	0.00	0.00
ATOM	683	CB	LEU	81	-7.852	-5.633	-11.088	0.00	0.00
ATOM	684	CG	LEU	81	-8.925	-6.361	-11.926	0.00	0.00
ATOM	685	CD1	LEU	81	-10.130	-6.825	-11.091	0.00	0.00
ATOM	686	CD2	LEU	81	-9.447	-5.431	-13.032	0.00	0.00
ATOM	687	H	LEU	81	-6.254	-7.229	-12.330	1.00	99.99
ATOM	688	N	CYS	82	-7.474	-8.790	-9.743	0.00	0.00
ATOM	689	CA	CYS	82	-7.870	-9.842	-8.815	0.00	0.00
ATOM	690	C	CYS	82	-6.773	-10.071	-7.771	0.00	0.00
ATOM	691	O	CYS	82	-7.084	-10.069	-6.581	0.00	0.00
ATOM	692	CB	CYS	82	-8.181	-11.122	-9.601	0.00	0.00
ATOM	693	SG	CYS	82	-8.822	-12.397	-8.483	0.00	0.00
ATOM	694	H	CYS	82	-7.232	-9.060	-10.685	1.00	99.99
ATOM	695	HG	CYS	82	-8.977	-13.342	-9.415	1.00	99.99
ATOM	696	N	ILE	83	-5.505	-10.239	-8.191	0.00	0.00
ATOM	697	CA	ILE	83	-4.407	-10.490	-7.258	0.00	0.00
ATOM	698	C	ILE	83	-4.147	-9.303	-6.326	0.00	0.00
ATOM	699	O	ILE	83	-3.876	-9.520	-5.147	0.00	0.00
ATOM	700	CB	ILE	83	-3.110	-11.018	-7.916	0.00	0.00
ATOM	701	CG1	ILE	83	-2.464	-10.029	-8.908	0.00	0.00
ATOM	702	CG2	ILE	83	-3.376	-12.398	-8.545	0.00	0.00
ATOM	703	CD1	ILE	83	-1.076	-10.449	-9.406	0.00	0.00
ATOM	704	H	ILE	83	-5.299	-10.228	-9.181	1.00	99.99
ATOM	705	N	SER	84	-4.295	-8.065	-6.815	0.00	0.00

ATOM	706	CA	SER	84	-4.185	-6.861	-5.999	0.00	0.00
ATOM	707	C	SER	84	-5.305	-6.788	-4.952	0.00	0.00
ATOM	708	O	SER	84	-5.040	-6.413	-3.811	0.00	0.00
ATOM	709	CB	SER	84	-4.229	-5.644	-6.931	0.00	0.00
ATOM	710	OG	SER	84	-4.021	-4.452	-6.205	0.00	0.00
ATOM	711	H	SER	84	-4.518	-7.952	-7.795	1.00	99.99
ATOM	712	HG	SER	84	-4.040	-3.713	-6.817	1.00	99.99
ATOM	713	N	VAL	85	-6.535	-7.178	-5.324	0.00	0.00
ATOM	714	CA	VAL	85	-7.690	-7.218	-4.428	0.00	0.00
ATOM	715	C	VAL	85	-7.544	-8.290	-3.334	0.00	0.00
ATOM	716	O	VAL	85	-8.061	-8.092	-2.235	0.00	0.00
ATOM	717	CB	VAL	85	-8.998	-7.352	-5.246	0.00	0.00
ATOM	718	CG1	VAL	85	-10.214	-7.827	-4.431	0.00	0.00
ATOM	719	CG2	VAL	85	-9.361	-5.986	-5.859	0.00	0.00
ATOM	720	H	VAL	85	-6.684	-7.476	-6.279	1.00	99.99
ATOM	721	N	LEU	86	-6.811	-9.385	-3.579	0.00	0.00
ATOM	722	CA	LEU	86	-6.530	-10.378	-2.544	0.00	0.00
ATOM	723	C	LEU	86	-5.603	-9.815	-1.462	0.00	0.00
ATOM	724	O	LEU	86	-5.867	-10.023	-0.277	0.00	0.00
ATOM	725	CB	LEU	86	-5.931	-11.656	-3.161	0.00	0.00
ATOM	726	CG	LEU	86	-6.917	-12.472	-4.025	0.00	0.00
ATOM	727	CD1	LEU	86	-6.158	-13.577	-4.772	0.00	0.00
ATOM	728	CD2	LEU	86	-8.036	-13.112	-3.188	0.00	0.00
ATOM	729	H	LEU	86	-6.409	-9.519	-4.497	1.00	99.99
ATOM	730	N	LEU	87	-4.555	-9.073	-1.855	0.00	0.00
ATOM	731	CA	LEU	87	-3.693	-8.366	-0.911	0.00	0.00
ATOM	732	C	LEU	87	-4.417	-7.191	-0.237	0.00	0.00
ATOM	733	O	LEU	87	-4.011	-6.796	0.855	0.00	0.00
ATOM	734	CB	LEU	87	-2.393	-7.889	-1.592	0.00	0.00
ATOM	735	CG	LEU	87	-1.291	-8.950	-1.828	0.00	0.00
ATOM	736	CD1	LEU	87	-0.956	-9.769	-0.571	0.00	0.00
ATOM	737	CD2	LEU	87	-1.575	-9.897	-2.998	0.00	0.00
ATOM	738	H	LEU	87	-4.386	-8.940	-2.843	1.00	99.99
ATOM	739	N	ALA	88	-5.496	-6.665	-0.837	0.00	0.00
ATOM	740	CA	ALA	88	-6.288	-5.590	-0.255	0.00	0.00
ATOM	741	C	ALA	88	-7.083	-6.048	0.972	0.00	0.00
ATOM	742	O	ALA	88	-7.166	-5.302	1.946	0.00	0.00
ATOM	743	CB	ALA	88	-7.211	-4.976	-1.305	0.00	0.00
ATOM	744	H	ALA	88	-5.776	-7.017	-1.742	1.00	99.99
ATOM	745	N	LEU	89	-7.629	-7.272	0.946	0.00	0.00
ATOM	746	CA	LEU	89	-8.274	-7.881	2.106	0.00	0.00
ATOM	747	C	LEU	89	-7.245	-8.364	3.140	0.00	0.00
ATOM	748	O	LEU	89	-7.584	-8.432	4.321	0.00	0.00
ATOM	749	CB	LEU	89	-9.186	-9.043	1.662	0.00	0.00
ATOM	750	CG	LEU	89	-10.632	-8.658	1.276	0.00	0.00
ATOM	751	CD1	LEU	89	-11.423	-8.092	2.468	0.00	0.00
ATOM	752	CD2	LEU	89	-10.716	-7.689	0.089	0.00	0.00
ATOM	753	H	LEU	89	-7.542	-7.830	0.106	1.00	99.99
ATOM	754	N	THR	90	-5.994	-8.643	2.734	0.00	0.00
ATOM	755	CA	THR	90	-4.900	-8.941	3.660	0.00	0.00
ATOM	756	C	THR	90	-4.597	-7.729	4.565	0.00	0.00
ATOM	757	O	THR	90	-4.396	-7.880	5.770	0.00	0.00
ATOM	758	CB	THR	90	-3.669	-9.491	2.901	0.00	0.00
ATOM	759	OG1	THR	90	-3.485	-10.845	3.257	0.00	0.00
ATOM	760	CG2	THR	90	-2.336	-8.768	3.142	0.00	0.00
ATOM	761	H	THR	90	-5.777	-8.588	1.748	1.00	99.99
ATOM	762	HG1	THR	90	-2.755	-11.198	2.741	1.00	99.99
ATOM	763	N	VAL	91	-4.622	-6.530	3.975	0.00	0.00
ATOM	764	CA	VAL	91	-4.453	-5.213	4.589	0.00	0.00
ATOM	765	C	VAL	91	-5.683	-4.789	5.417	0.00	0.00
ATOM	766	O	VAL	91	-5.598	-3.869	6.228	0.00	0.00
ATOM	767	CB	VAL	91	-4.233	-4.161	3.507	0.00	99.99
ATOM	768	CG1	VAL	91	-4.404	-2.769	4.110	0.00	99.99
ATOM	769	CG2	VAL	91	-2.825	-4.298	2.941	0.00	99.99
ATOM	770	N	PHE	92	-6.842	-5.423	5.194	0.00	0.00

ATOM	771	CA	PHE	92	-8.094	-5.092	5.865	0.00	0.00
ATOM	772	C	PHE	92	-8.318	-5.951	7.113	0.00	0.00
ATOM	773	O	PHE	92	-8.996	-5.514	8.038	0.00	0.00
ATOM	774	CB	PHE	92	-9.244	-5.283	4.865	0.00	0.00
ATOM	775	CG	PHE	92	-10.588	-4.770	5.342	0.00	0.00
ATOM	776	CD1	PHE	92	-11.566	-5.666	5.815	0.00	0.00
ATOM	777	CD2	PHE	92	-10.866	-3.390	5.305	0.00	0.00
ATOM	778	CE1	PHE	92	-12.813	-5.182	6.250	0.00	0.00
ATOM	779	CE2	PHE	92	-12.107	-2.905	5.751	0.00	0.00
ATOM	780	CZ	PHE	92	-13.082	-3.802	6.223	0.00	0.00
ATOM	781	H	PHE	92	-6.868	-6.154	4.498	1.00	99.99
ATOM	782	N	LEU	93	-7.720	-7.147	7.170	0.00	0.00
ATOM	783	CA	LEU	93	-7.607	-7.931	8.393	0.00	0.00
ATOM	784	C	LEU	93	-6.476	-7.392	9.286	0.00	0.00
ATOM	785	O	LEU	93	-6.534	-7.605	10.495	0.00	0.00
ATOM	786	CB	LEU	93	-7.337	-9.401	8.029	0.00	0.00
ATOM	787	CG	LEU	93	-8.505	-10.093	7.292	0.00	0.00
ATOM	788	CD1	LEU	93	-8.049	-11.471	6.794	0.00	0.00
ATOM	789	CD2	LEU	93	-9.743	-10.260	8.187	0.00	0.00
ATOM	790	H	LEU	93	-7.216	-7.478	6.358	1.00	99.99
ATOM	791	N	LEU	94	-5.492	-6.665	8.716	0.00	0.00
ATOM	792	CA	LEU	94	-4.451	-5.952	9.457	0.00	0.00
ATOM	793	C	LEU	94	-5.090	-4.966	10.421	0.00	0.00
ATOM	794	O	LEU	94	-4.900	-5.085	11.631	0.00	0.00
ATOM	795	CB	LEU	94	-3.480	-5.226	8.501	0.00	0.00
ATOM	796	CG	LEU	94	-2.353	-4.352	9.118	0.00	0.00
ATOM	797	CD1	LEU	94	-1.439	-3.925	7.963	0.00	0.00
ATOM	798	CD2	LEU	94	-2.778	-3.049	9.821	0.00	0.00
ATOM	799	H	LEU	94	-5.499	-6.553	7.712	1.00	99.99
ATOM	800	N	LEU	95	-5.820	-3.984	9.872	0.00	0.00
ATOM	801	CA	LEU	95	-6.449	-2.929	10.650	0.00	0.00
ATOM	802	C	LEU	95	-7.493	-3.521	11.603	0.00	0.00
ATOM	803	O	LEU	95	-7.759	-2.920	12.628	0.00	0.00
ATOM	804	CB	LEU	95	-7.031	-1.860	9.702	0.00	0.00
ATOM	805	CG	LEU	95	-8.254	-2.255	8.847	0.00	0.00
ATOM	806	CD1	LEU	95	-9.593	-1.964	9.540	0.00	0.00
ATOM	807	CD2	LEU	95	-8.260	-1.499	7.512	0.00	0.00
ATOM	808	H	LEU	95	-5.919	-3.951	8.867	1.00	99.99
ATOM	809	N	ILE	96	-8.050	-4.708	11.327	0.00	0.00
ATOM	810	CA	ILE	96	-9.022	-5.369	12.197	0.00	0.00
ATOM	811	C	ILE	96	-8.387	-6.082	13.410	0.00	0.00
ATOM	812	O	ILE	96	-9.102	-6.439	14.344	0.00	0.00
ATOM	813	CB	ILE	96	-9.920	-6.295	11.322	0.00	0.00
ATOM	814	CG1	ILE	96	-10.979	-5.416	10.613	0.00	0.00
ATOM	815	CG2	ILE	96	-10.612	-7.453	12.070	0.00	0.00
ATOM	816	CD1	ILE	96	-11.868	-6.145	9.597	0.00	0.00
ATOM	817	H	ILE	96	-7.793	-5.180	10.472	1.00	99.99
ATOM	818	N	SER	97	-7.059	-6.234	13.455	0.00	0.00
ATOM	819	CA	SER	97	-6.334	-6.780	14.606	0.00	0.00
ATOM	820	C	SER	97	-5.306	-5.798	15.185	0.00	0.00
ATOM	821	O	SER	97	-4.693	-6.100	16.208	0.00	0.00
ATOM	822	CB	SER	97	-5.760	-8.160	14.256	0.00	0.00
ATOM	823	OG	SER	97	-5.015	-8.132	13.060	0.00	0.00
ATOM	824	H	SER	97	-6.507	-5.963	12.651	1.00	99.99
ATOM	825	HG	SER	97	-4.783	-9.033	12.822	1.00	99.99
ATOM	826	N	LYS	98	-5.198	-4.596	14.597	0.00	0.00
ATOM	827	CA	LYS	98	-4.651	-3.399	15.233	0.00	0.00
ATOM	828	C	LYS	98	-5.757	-2.436	15.696	0.00	0.00
ATOM	829	O	LYS	98	-5.464	-1.551	16.499	0.00	0.00
ATOM	830	CB	LYS	98	-3.647	-2.714	14.287	0.00	0.00
ATOM	831	CG	LYS	98	-2.211	-3.185	14.574	0.00	0.00
ATOM	832	CD	LYS	98	-1.468	-2.332	15.616	0.00	0.00
ATOM	833	CE	LYS	98	-2.219	-2.091	16.926	0.00	0.00
ATOM	834	NZ	LYS	98	-1.576	-1.033	17.722	0.00	0.00
ATOM	835	H	LYS	98	-5.681	-4.458	13.721	1.00	99.99

ATOM	836	HZ1	LYS	98	-1.606	-0.172	17.188	1.00	99.99
ATOM	837	HZ2	LYS	98	-2.081	-0.902	18.587	1.00	99.99
ATOM	838	HZ3	LYS	98	-0.617	-1.281	17.915	1.00	99.99
ATOM	839	N	ILE	99	-7.014	-2.629	15.257	0.00	0.00
ATOM	840	CA	ILE	99	-8.183	-1.910	15.761	0.00	0.00
ATOM	841	C	ILE	99	-9.354	-2.838	16.111	0.00	0.00
ATOM	842	O	ILE	99	-9.812	-2.824	17.253	0.00	0.00
ATOM	843	CB	ILE	99	-8.578	-0.611	14.993	0.00	0.00
ATOM	844	CG1	ILE	99	-9.986	-0.568	14.330	0.00	0.00
ATOM	845	CG2	ILE	99	-7.440	-0.024	14.128	0.00	0.00
ATOM	846	CD1	ILE	99	-10.151	-1.102	12.907	0.00	0.00
ATOM	847	H	ILE	99	-7.181	-3.351	14.572	1.00	99.99
HETATM	848	N	NME	100	-9.856	-3.612	15.142	0.00	0.00
HETATM	849	H	NME	100	-9.425	-3.578	14.228	0.00	0.00
HETATM	850	CA	NME	100	-11.085	-4.380	15.281	0.00	0.00
ATOM	851	N	GLU	102	5.788	-7.211	-17.481	0.00	0.00
ATOM	852	CA	GLU	102	4.848	-7.189	-16.356	0.00	0.00
ATOM	853	C	GLU	102	4.997	-8.397	-15.412	0.00	0.00
ATOM	854	O	GLU	102	4.547	-8.337	-14.272	0.00	0.00
ATOM	855	CB	GLU	102	3.417	-7.059	-16.912	0.00	0.00
ATOM	856	CG	GLU	102	2.315	-6.884	-15.850	0.00	0.00
ATOM	857	CD	GLU	102	2.611	-5.777	-14.830	0.00	0.00
ATOM	858	OE1	GLU	102	2.451	-6.055	-13.621	0.00	0.00
ATOM	859	OE2	GLU	102	3.004	-4.674	-15.270	0.00	0.00
ATOM	860	H	GLU	102	5.386	-7.173	-18.406	1.00	99.99
ATOM	861	N	LYS	103	5.656	-9.477	-15.853	0.00	0.00
ATOM	862	CA	LYS	103	5.855	-10.692	-15.071	0.00	0.00
ATOM	863	C	LYS	103	6.870	-10.507	-13.939	0.00	0.00
ATOM	864	O	LYS	103	6.650	-11.020	-12.842	0.00	0.00
ATOM	865	CB	LYS	103	6.292	-11.843	-15.997	0.00	0.00
ATOM	866	CG	LYS	103	5.142	-12.514	-16.771	0.00	0.00
ATOM	867	CD	LYS	103	4.455	-11.619	-17.817	0.00	0.00
ATOM	868	CE	LYS	103	3.415	-12.388	-18.642	0.00	0.00
ATOM	869	NZ	LYS	103	4.035	-13.385	-19.536	0.00	0.00
ATOM	870	H	LYS	103	6.027	-9.457	-16.791	1.00	99.99
ATOM	871	HZ1	LYS	103	4.552	-14.058	-18.988	1.00	99.99
ATOM	872	HZ2	LYS	103	3.316	-13.863	-20.062	1.00	99.99
ATOM	873	HZ3	LYS	103	4.664	-12.922	-20.177	1.00	99.99
ATOM	874	N	MET	104	7.961	-9.768	-14.185	0.00	0.00
ATOM	875	CA	MET	104	8.896	-9.366	-13.138	0.00	0.00
ATOM	876	C	MET	104	8.305	-8.224	-12.304	0.00	0.00
ATOM	877	O	MET	104	8.615	-8.137	-11.120	0.00	0.00
ATOM	878	CB	MET	104	10.229	-8.957	-13.787	0.00	0.00
ATOM	879	CG	MET	104	11.329	-8.633	-12.766	0.00	0.00
ATOM	880	SD	MET	104	11.730	-9.976	-11.612	0.00	0.00
ATOM	881	CE	MET	104	13.090	-9.197	-10.705	0.00	0.00
ATOM	882	H	MET	104	8.084	-9.368	-15.104	1.00	99.99
ATOM	883	N	THR	105	7.436	-7.383	-12.888	0.00	0.00
ATOM	884	CA	THR	105	6.771	-6.285	-12.189	0.00	0.00
ATOM	885	C	THR	105	5.844	-6.813	-11.088	0.00	0.00
ATOM	886	O	THR	105	5.914	-6.335	-9.955	0.00	0.00
ATOM	887	CB	THR	105	5.997	-5.394	-13.179	0.00	0.00
ATOM	888	OG1	THR	105	6.855	-4.945	-14.208	0.00	0.00
ATOM	889	CG2	THR	105	5.397	-4.156	-12.502	0.00	0.00
ATOM	890	H	THR	105	7.231	-7.492	-13.872	1.00	99.99
ATOM	891	HG1	THR	105	6.350	-4.365	-14.783	1.00	99.99
ATOM	892	N	LEU	106	4.997	-7.805	-11.402	0.00	0.00
ATOM	893	CA	LEU	106	4.120	-8.434	-10.420	0.00	0.00
ATOM	894	C	LEU	106	4.886	-9.297	-9.415	0.00	0.00
ATOM	895	O	LEU	106	4.414	-9.452	-8.293	0.00	0.00
ATOM	896	CB	LEU	106	2.946	-9.161	-11.107	0.00	0.00
ATOM	897	CG	LEU	106	3.285	-10.405	-11.958	0.00	0.00
ATOM	898	CD1	LEU	106	3.360	-11.700	-11.133	0.00	0.00
ATOM	899	CD2	LEU	106	2.220	-10.598	-13.048	0.00	0.00
ATOM	900	H	LEU	106	4.955	-8.138	-12.357	1.00	99.99

ATOM	901	N	CYS	107	6.076	-9.802	-9.775	0.00	0.00
ATOM	902	CA	CYS	107	6.959	-10.502	-8.851	0.00	0.00
ATOM	903	C	CYS	107	7.514	-9.531	-7.807	0.00	0.00
ATOM	904	O	CYS	107	7.409	-9.826	-6.618	0.00	0.00
ATOM	905	CB	CYS	107	8.082	-11.186	-9.642	0.00	0.00
ATOM	906	SG	CYS	107	9.106	-12.185	-8.530	0.00	0.00
ATOM	907	H	CYS	107	6.410	-9.644	-10.715	1.00	99.99
ATOM	908	HG	CYS	107	9.956	-12.618	-9.466	1.00	99.99
ATOM	909	N	ILE	108	8.071	-8.379	-8.226	0.00	0.00
ATOM	910	CA	ILE	108	8.642	-7.413	-7.290	0.00	0.00
ATOM	911	C	ILE	108	7.585	-6.825	-6.352	0.00	0.00
ATOM	912	O	ILE	108	7.856	-6.698	-5.162	0.00	0.00
ATOM	913	CB	ILE	108	9.539	-6.330	-7.938	0.00	0.00
ATOM	914	CG1	ILE	108	8.800	-5.405	-8.926	0.00	0.00
ATOM	915	CG2	ILE	108	10.773	-6.998	-8.571	0.00	0.00
ATOM	916	CD1	ILE	108	9.621	-4.198	-9.395	0.00	0.00
ATOM	917	H	ILE	108	8.128	-8.179	-9.216	1.00	99.99
ATOM	918	N	SER	109	6.372	-6.546	-6.845	0.00	0.00
ATOM	919	CA	SER	109	5.265	-6.074	-6.021	0.00	0.00
ATOM	920	C	SER	109	4.848	-7.120	-4.978	0.00	0.00
ATOM	921	O	SER	109	4.563	-6.754	-3.839	0.00	0.00
ATOM	922	CB	SER	109	4.092	-5.731	-6.947	0.00	0.00
ATOM	923	OG	SER	109	3.028	-5.162	-6.216	0.00	0.00
ATOM	924	H	SER	109	6.205	-6.679	-7.834	1.00	99.99
ATOM	925	HG	SER	109	2.317	-4.947	-6.824	1.00	99.99
ATOM	926	N	VAL	110	4.849	-8.412	-5.349	0.00	0.00
ATOM	927	CA	VAL	110	4.526	-9.523	-4.455	0.00	0.00
ATOM	928	C	VAL	110	5.595	-9.736	-3.370	0.00	0.00
ATOM	929	O	VAL	110	5.249	-10.185	-2.278	0.00	0.00
ATOM	930	CB	VAL	110	4.228	-10.801	-5.279	0.00	0.00
ATOM	931	CG1	VAL	110	4.290	-12.110	-4.473	0.00	0.00
ATOM	932	CG2	VAL	110	2.814	-10.701	-5.883	0.00	0.00
ATOM	933	H	VAL	110	5.095	-8.644	-6.301	1.00	99.99
ATOM	934	N	LEU	111	6.864	-9.373	-3.610	0.00	0.00
ATOM	935	CA	LEU	111	7.889	-9.415	-2.568	0.00	0.00
ATOM	936	C	LEU	111	7.591	-8.396	-1.466	0.00	0.00
ATOM	937	O	LEU	111	7.632	-8.750	-0.288	0.00	0.00
ATOM	938	CB	LEU	111	9.294	-9.189	-3.157	0.00	0.00
ATOM	939	CG	LEU	111	9.802	-10.327	-4.068	0.00	0.00
ATOM	940	CD1	LEU	111	11.103	-9.891	-4.757	0.00	0.00
ATOM	941	CD2	LEU	111	10.057	-11.628	-3.292	0.00	0.00
ATOM	942	H	LEU	111	7.116	-9.015	-4.521	1.00	99.99
ATOM	943	N	LEU	112	7.252	-7.156	-1.847	0.00	0.00
ATOM	944	CA	LEU	112	6.854	-6.108	-0.913	0.00	0.00
ATOM	945	C	LEU	112	5.460	-6.346	-0.311	0.00	0.00
ATOM	946	O	LEU	112	5.132	-5.721	0.698	0.00	0.00
ATOM	947	CB	LEU	112	6.958	-4.728	-1.587	0.00	0.00
ATOM	948	CG	LEU	112	8.387	-4.206	-1.871	0.00	0.00
ATOM	949	CD1	LEU	112	9.353	-4.393	-0.688	0.00	0.00
ATOM	950	CD2	LEU	112	9.042	-4.756	-3.139	0.00	0.00
ATOM	951	H	LEU	112	7.233	-6.937	-2.834	1.00	99.99
ATOM	952	N	ALA	113	4.666	-7.274	-0.866	0.00	0.00
ATOM	953	CA	ALA	113	3.404	-7.696	-0.277	0.00	0.00
ATOM	954	C	ALA	113	3.618	-8.559	0.969	0.00	0.00
ATOM	955	O	ALA	113	2.930	-8.356	1.969	0.00	0.00
ATOM	956	CB	ALA	113	2.547	-8.426	-1.311	0.00	0.00
ATOM	957	H	ALA	113	4.973	-7.744	-1.706	1.00	99.99
ATOM	958	N	LEU	114	4.583	-9.491	0.927	0.00	0.00
ATOM	959	CA	LEU	114	4.974	-10.298	2.081	0.00	0.00
ATOM	960	C	LEU	114	5.779	-9.482	3.103	0.00	0.00
ATOM	961	O	LEU	114	5.748	-9.823	4.285	0.00	0.00
ATOM	962	CB	LEU	114	5.771	-11.536	1.621	0.00	0.00
ATOM	963	CG	LEU	114	4.931	-12.778	1.245	0.00	0.00
ATOM	964	CD1	LEU	114	4.166	-13.350	2.450	0.00	0.00
ATOM	965	CD2	LEU	114	3.961	-12.538	0.081	0.00	0.00

ATOM	966	H	LEU	114	5.105	-9.614	0.070	1.00	99.99
ATOM	967	N	THR	115	6.437	-8.388	2.684	0.00	0.00
ATOM	968	CA	THR	115	7.061	-7.429	3.597	0.00	0.00
ATOM	969	C	THR	115	6.004	-6.808	4.520	0.00	0.00
ATOM	970	O	THR	115	6.203	-6.724	5.732	0.00	0.00
ATOM	971	CB	THR	115	7.850	-6.357	2.822	0.00	0.00
ATOM	972	OG1	THR	115	8.856	-6.976	2.049	0.00	0.00
ATOM	973	CG2	THR	115	8.536	-5.343	3.744	0.00	0.00
ATOM	974	H	THR	115	6.462	-8.179	1.695	1.00	99.99
ATOM	975	HG1	THR	115	9.358	-6.292	1.600	1.00	99.99
ATOM	976	N	VAL	116	4.865	-6.420	3.937	0.00	0.00
ATOM	977	CA	VAL	116	3.714	-5.834	4.610	0.00	0.00
ATOM	978	C	VAL	116	2.840	-6.870	5.349	0.00	0.00
ATOM	979	O	VAL	116	1.930	-6.491	6.087	0.00	0.00
ATOM	980	CB	VAL	116	2.821	-5.132	3.593	0.00	99.99
ATOM	981	CG1	VAL	116	1.467	-4.828	4.229	0.00	99.99
ATOM	982	CG2	VAL	116	3.477	-3.829	3.151	0.00	99.99
ATOM	983	N	PHE	117	3.110	-8.171	5.174	0.00	0.00
ATOM	984	CA	PHE	117	2.400	-9.253	5.851	0.00	0.00
ATOM	985	C	PHE	117	3.141	-9.726	7.108	0.00	0.00
ATOM	986	O	PHE	117	2.504	-10.191	8.048	0.00	0.00
ATOM	987	CB	PHE	117	2.221	-10.413	4.862	0.00	0.00
ATOM	988	CG	PHE	117	1.273	-11.497	5.337	0.00	0.00
ATOM	989	CD1	PHE	117	1.772	-12.711	5.847	0.00	0.00
ATOM	990	CD2	PHE	117	-0.117	-11.289	5.264	0.00	0.00
ATOM	991	CE1	PHE	117	0.881	-13.709	6.281	0.00	0.00
ATOM	992	CE2	PHE	117	-1.006	-12.283	5.705	0.00	0.00
ATOM	993	CZ	PHE	117	-0.507	-13.495	6.215	0.00	0.00
ATOM	994	H	PHE	117	3.853	-8.430	4.541	1.00	99.99
ATOM	995	N	LEU	118	4.470	-9.571	7.159	0.00	0.00
ATOM	996	CA	LEU	118	5.248	-9.706	8.388	0.00	0.00
ATOM	997	C	LEU	118	5.076	-8.470	9.290	0.00	0.00
ATOM	998	O	LEU	118	5.266	-8.568	10.503	0.00	0.00
ATOM	999	CB	LEU	118	6.733	-9.887	8.025	0.00	0.00
ATOM	1000	CG	LEU	118	7.045	-11.202	7.277	0.00	0.00
ATOM	1001	CD1	LEU	118	8.486	-11.161	6.750	0.00	0.00
ATOM	1002	CD2	LEU	118	6.867	-12.436	8.174	0.00	0.00
ATOM	1003	H	LEU	118	4.952	-9.227	6.340	1.00	99.99
ATOM	1004	N	LEU	119	4.684	-7.327	8.702	0.00	0.00
ATOM	1005	CA	LEU	119	4.344	-6.095	9.399	0.00	0.00
ATOM	1006	C	LEU	119	3.168	-6.312	10.329	0.00	0.00
ATOM	1007	O	LEU	119	3.315	-6.088	11.531	0.00	0.00
ATOM	1008	CB	LEU	119	4.091	-4.980	8.368	0.00	0.00
ATOM	1009	CG	LEU	119	3.542	-3.613	8.849	0.00	0.00
ATOM	1010	CD1	LEU	119	3.637	-2.659	7.650	0.00	0.00
ATOM	1011	CD2	LEU	119	2.071	-3.607	9.296	0.00	0.00
ATOM	1012	H	LEU	119	4.577	-7.325	7.698	1.00	99.99
ATOM	1013	N	LEU	120	2.020	-6.742	9.780	0.00	0.00
ATOM	1014	CA	LEU	120	0.847	-7.006	10.594	0.00	0.00
ATOM	1015	C	LEU	120	1.196	-8.082	11.617	0.00	0.00
ATOM	1016	O	LEU	120	0.868	-7.887	12.770	0.00	0.00
ATOM	1017	CB	LEU	120	-0.389	-7.303	9.718	0.00	0.00
ATOM	1018	CG	LEU	120	-0.420	-8.605	8.891	0.00	0.00
ATOM	1019	CD1	LEU	120	-1.031	-9.789	9.656	0.00	0.00
ATOM	1020	CD2	LEU	120	-1.238	-8.408	7.606	0.00	0.00
ATOM	1021	H	LEU	120	1.965	-6.893	8.783	1.00	99.99
ATOM	1022	N	ILE	121	1.952	-9.132	11.261	0.00	0.00
ATOM	1023	CA	ILE	121	2.309	-10.226	12.171	0.00	0.00
ATOM	1024	C	ILE	121	3.063	-9.794	13.437	0.00	0.00
ATOM	1025	O	ILE	121	2.951	-10.474	14.455	0.00	0.00
ATOM	1026	CB	ILE	121	3.044	-11.338	11.371	0.00	0.00
ATOM	1027	CG1	ILE	121	1.996	-12.159	10.582	0.00	0.00
ATOM	1028	CG2	ILE	121	3.910	-12.280	12.235	0.00	0.00
ATOM	1029	CD1	ILE	121	2.583	-13.151	9.570	0.00	0.00
ATOM	1030	H	ILE	121	2.237	-9.221	10.296	1.00	99.99

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ATOM    1031  N    SER   122       3.779  -8.666  13.408  0.00  0.00
ATOM    1032  CA   SER   122       4.547  -8.154  14.544  0.00  0.00
ATOM    1033  C    SER   122       3.910  -6.923  15.201  0.00  0.00
ATOM    1034  O    SER   122       4.356  -6.504  16.269  0.00  0.00
ATOM    1035  CB   SER   122       5.983  -7.919  14.082  0.00  0.00
ATOM    1036  OG   SER   122       6.054  -6.966  13.038  0.00  0.00
ATOM    1037  H    SER   122       3.814  -8.140  12.545  1.00 99.99
ATOM    1038  HG   SER   122       5.710  -7.367  12.233  1.00 99.99
ATOM    1039  N    LYS   123       2.824  -6.407  14.610  0.00  0.00
ATOM    1040  CA   LYS   123       1.865  -5.507  15.238  0.00  0.00
ATOM    1041  C    LYS   123       0.606  -6.239  15.731  0.00  0.00
ATOM    1042  O    LYS   123      -0.209  -5.615  16.411  0.00  0.00
ATOM    1043  CB   LYS   123       1.524  -4.373  14.258  0.00  0.00
ATOM    1044  CG   LYS   123       2.444  -3.153  14.412  0.00  0.00
ATOM    1045  CD   LYS   123       2.457  -2.557  15.837  0.00  0.00
ATOM    1046  CE   LYS   123       3.740  -2.934  16.588  0.00  0.00
ATOM    1047  NZ   LYS   123       3.804  -2.279  17.906  0.00  0.00
ATOM    1048  H    LYS   123       2.554  -6.785  13.712  1.00 99.99
ATOM    1049  HZ1  LYS   123       3.039  -2.591  18.485  1.00 99.99
ATOM    1050  HZ2  LYS   123       4.684  -2.505  18.349  1.00 99.99
ATOM    1051  HZ3  LYS   123       3.755  -1.276  17.784  1.00 99.99
ATOM    1052  N    ILE   124       0.460  -7.540  15.426  0.00  0.00
ATOM    1053  CA   ILE   124      -0.713  -8.357  15.735  0.00  0.00
ATOM    1054  C    ILE   124      -0.378  -9.710  16.388  0.00  0.00
ATOM    1055  O    ILE   124      -1.293 -10.446  16.758  0.00  0.00
ATOM    1056  CB   ILE   124      -1.737  -8.470  14.570  0.00  0.00
ATOM    1057  CG1  ILE   124      -1.402  -9.547  13.510  0.00  0.00
ATOM    1058  CG2  ILE   124      -2.030  -7.099  13.925  0.00  0.00
ATOM    1059  CD1  ILE   124      -2.384 -10.723  13.496  0.00  0.00
ATOM    1060  H    ILE   124       1.160  -7.964  14.834  1.00 99.99
ATOM    1061  H    ILE   124       1.160  -7.964  14.834  1.00 99.99
HETATM  1062  N    NME   125       0.912 -10.026  16.573  0.00  0.00
HETATM  1063  H    NME   125       1.620  -9.385  16.248  0.00  0.00
HETATM  1064  CA   NME   125       1.375 -11.257  17.196  0.00  0.00
CONECT  210  211  212
CONECT  423  424  425
CONECT  635  636  637
CONECT  848  849  850
CONECT 1062 1063 1064
SPDBVT         1.0000000000           0.0000000000           0.0000000000
SPDBVT         0.0000000000           1.0000000000           0.0000000000
SPDBVT         0.0000000000           0.0000000000           1.0000000000
SPDBVT         0.0000000000           0.0000000000           0.0000000000
SPDBVT         0.0000000000           0.0000000000           0.0000000000
SPDBVV default;
SPDBVV       8.228955557850    1111.571236645071      20.000000000000
SPDBVV         0.9458704269          -0.2510394381          -0.2056899028
SPDBVV        -0.2749012337          -0.9566045536          -0.0966283586
SPDBVV        -0.1725063688           0.1479423148          -0.9738350087
SPDBVV        -0.2540000081           0.0170000009          -0.6704999804
SPDBVV         0.0000000000           0.0000000000           0.0000000000
SPDBVf  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3
SPDBVf  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3
SPDBVf  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3
SPDBVf  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3
SPDBVf  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3
SPDBVf  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3  3
SPDBVl 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00
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SPDBVl 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00
SPDBVl 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00 1.00
SPDBVb 0.00 0.00 0.20
END
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